(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 376 079**
A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 89123159.9

(22) Date of filing: 14.12.89

(51) Int. Cl.5: C07D 237/22, A61K 31/50, C07D 405/12, C07D 409/12, C07D 401/12

(30) Priority: 20.12.88 JP 321476/88
20.10.89 JP 274661/89

(43) Date of publication of application:
04.07.90 Bulletin 90/27

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

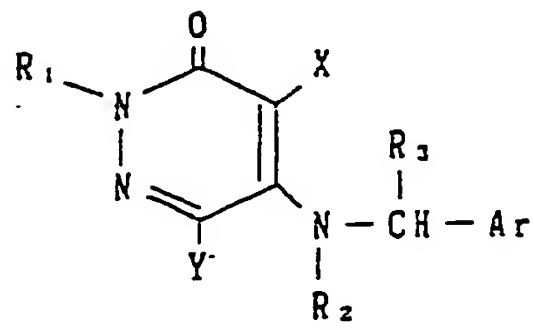
(71) Applicant: NISSAN CHEMICAL INDUSTRIES LTD.
7-1, 3-chome Kanda-Nishiki-cho
Chiyoda-ku Tokyo(JP)

(72) Inventor: Tanikawa, Keizo Nissan Chemical Industries Ltd.
Chuo Kenkyusho 722-1, Tsuboi-cho
Funabashi-shi Chiba-ken(JP)
Inventor: Sakoda, Ryozo Nissan Chemical Industries Ltd.
Chuo Kenkyusho 722-1, Tsuboi-cho
Funabashi-shi Chiba-ken(JP)
Inventor: Tanaka, Sakuya Nissan Chemical Ind. Ltd. Seibutsu
Kagaku Kenkyusho 1470,Oaza-shiraoka
Shiraoka-machi
Minamisaitama-gun Saitama-ken(JP)
Inventor: Shikada, Kenichi Nissan Chemical Ind. Ltd Seibutsu
Kagaku Kenkyusho 1470,Oaza-shiraoka
Shiraoka-machi
Minamisaitama-gun Saitama-ken(JP)

(74) Representative: Wächtershäuser, Günter, Dr.
Tal 29
D-8000 München 2(DE)

(54) 3(2H)pyridazinones, processes for their preparation and antagonistic agent against SRS-A.

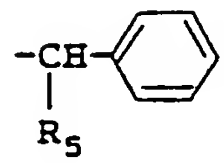
(57) A 3(2H)pyridazinone of the formula:



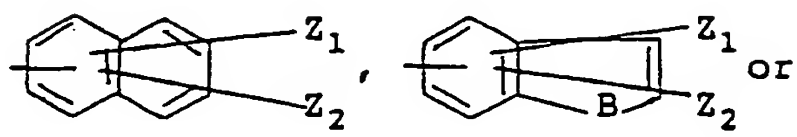
(I)

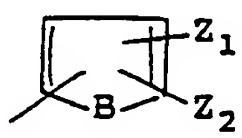
wherein R_1 is hydrogen, 2-propenyl, or straight chained or branched C_1-C_4 alkyl; each of R_2 and R_3 which may be the same or different, is hydrogen, or straight chained or branched C_1-C_3 alkyl; X is chlorine, or bromine; Y is hydrogen, halogen, nitro, amino, or $-AR_4$ wherein A is oxygen, or sulfur, and R_4 is hydrogen, straight chained, branched or cyclic C_1-C_8 alkyl, or

EP 0 376 079 A1



wherein R_5 is hydrogen, or straight chained or branched C_1-C_4 alkyl; and Ar is





wherein each of Z_1 and Z_2 which may be the same or different, is hydrogen, halogen, straight or branched C_1-C_4 alkyl, or -OR_6 wherein R_6 is straight or branched C_1-C_4 alkyl, and B is oxygen, sulfur, or -N=C- (to form a quinoline or pyridine ring); or a pharmaceutically acceptable salt thereof.

3(2H)PYRIDAZINONES, PROCESSES FOR THEIR PREPARATION AND ANTAGONISTIC AGENT AGAINST SRS-A

The present invention relates to novel 3(2H)pyridazinones and pharmaceutically acceptable salts thereof which exhibit antagonism against slow reacting substance of anaphylaxis (SRS-A), processes for their preparation and pharmaceutical compositions containing them as active ingredients.

SRS-A is a chemical mediator released together with histamine, etc. by an allergic reaction and has pharmacological activity to cause a strong and prolonged contraction of bronchial smooth muscle. It has long been known from such a phenomenal aspect. It was found in 1979 that SRS-A itself is a mixture of leukotriene C_4 (hereinafter referred to as LTC_4), leukotriene D_4 (hereinafter referred to as LTD_4) and leukotriene E_4 (hereinafter referred to as LTE_4) [generally called peptide leukotriene]. Extensive researches have been conducted on SRS-A for its relationship with acosmia. As a result, the relationship of SRS-A with immediate type allergic diseases such as bronchial asthma, allergic rhinitis, urticaria and hay fever, has become clear. Further, the relationship of SRS-A with various inflammatory diseases, ischemic heart diseases, etc., has been suggested. Therefore, a compound which exhibits antagonism against SRS-A, is expected to be useful as a prophylactic or thereapeutic drug against the affections caused by either LTC_4, LTD_4 or LTE_4, or by a mixture thereof.

As the antagonists against SRS-A, FPL-55712 (Fisons Limited) and its structural analogues as well as some medicinal substances, have been reported. (Agents and Actions, Vol 9, p. 133-140 (1979), Annual Reports in Medicinal Chemistry, Vol 20, p. 71-81 (1985) and Agents and Actions, Vol 18, p 332-341 (1986)) However, no instance of their practical application has been reported.

Now, the relationship of 3(2H)pyridazinones of the formula I and pharmaceutically acceptable salt thereof according to the present invention with compounds disclosed in published references will be described.

Canadian Patent No 784,639 (hereinafter referred to as reference (a)) discloses 3(2H)pyridazinone derivatives having hydrogen, C_1-C_8 alkyl, phenyl or C_3-C_8 cycloalkyl at 2-position, chlorine or bromine at 4-position and benzylamino at 5-position. However, the reference has no Examples corresponding to the compounds of the present invention, and the application of the compounds disclosed in this reference (a) is restricted to a herbicide, and no mention is made as to their medical use or pharmacological activities.

Chemical Abstract, 62, 2773b, (Bull. Soc. Chim, France, 1964 (9) p 2124-32 (reference (b)) discloses 3-(2H)pyridazinones having hydrogen or diethylaminoethyl at 2-position, chlorine at 4-position and benzylamino at 5-position. However, this reference (b) has no Examples corresponding to the compound of the present invention, and it is silent about medical use or pharmacological activities.

German Patent Application No 1,670,169 published on November 5, 1970 (reference (c)) discloses 3(2)-pyridazinones having hydrogen or an aliphatic, cycloaliphatic, araliphatic or aromatic group at 2-position, chlorine or bromine at 4-position and aralkylamino at 5-position. This reference (c) discloses a process for the synthesis of pyridazinones including such compounds, their application to agricultural chemicals, their application as intermediates for medicines or dyestuffs, or their application as intermediates for various compounds. However, no mention is made to their pharmacological activities, and no specific examples are given for such compounds. Further, such compounds are not specifically described.

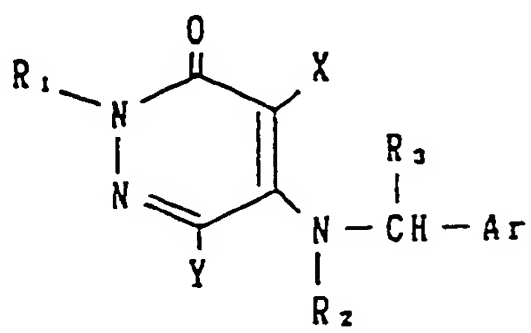
Angew. Chem. International Edition, Vol. 4, p. 292- 300 (1965) (reference (d)) discloses 3(2H)-pyridazinones having hydrogen at 2-position, chlorine at 4-position and N-methyl-benzylamino at 5-position. However, this reference (d) has no Examples corresponding to the compounds of the present invention, and no mention is made as to medical use or pharmacological activities.

The present inventors have conducted extensive researches with an object to find compounds which exhibit antagonism against SRS-A. They have found that 5-substituted benzylamino-6-unsubstituted or 6-substituted 3(2)pyridazinone derivatives having various functional groups and substitution modes, attain the above object, and have already filed patent applications (Japanese Unexamined Patent Publication No. 267560/1986 (reference (e)), Japanese Unexamined Patent Publication No. 30769/1987 (reference (f)) and European Patent 275,997 (reference (g)). However, the compounds disclosed in these references (e), (f) and (g) are all restricted to those wherein the 5-position of the 3(2H)pyridazinone ring is a substituted benzylamino group and contains no other aromatic methylamino group.

The present inventors have then conducted extensive researches on compounds having antagonistic activities against SRS-A, and it has been surprisingly found that 3(2H)pyridazinones of the formula I and their pharmacologically acceptable salts of the present invention are more excellent in the antagonistic activities against SRS-A than any compounds disclosed in references (a) to (g), and that they are useful as active ingredients for prophylactic or thereapeutic drugs against diseases caused by LTC_4, LTD_4 or LTE_4,

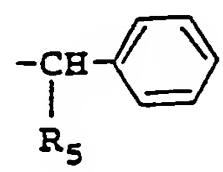
or by a mixture thereof which is a component of SRS-A. The present invention has been accomplished on the basis of this discovery.

The present invention provides a 3(2H)pyridazinone of the formula:

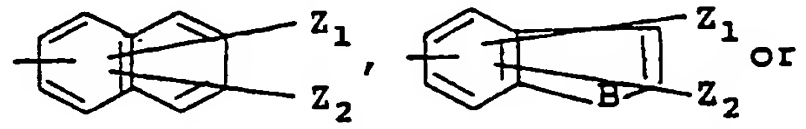


(I)

wherein R_1 is hydrogen, 2-propenyl, or straight chained or branched C_1-C_4 alkyl; each of R_2 and R_3 which may be the same or different, is hydrogen, or straight chained or branched C_1-C_3 alkyl; X is chlorine, or bromine; Y is hydrogen, halogen, nitro, amino, or $-AR_4$ wherein A is oxygen, or sulfur, and R_4 is hydrogen, straight chained, branched or cyclic C_1-C_8 alkyl, or



wherein R_5 is hydrogen, or straight chained or branched C_1-C_4 alkyl; and Ar is



wherein each of Z_1 and Z_2 which may be the same or different, is hydrogen, halogen, straight or branched C_1-C_4 alkyl, or $-OR_6$ wherein R_6 is straight or branched C_1-C_4 alkyl, and B is oxygen, sulfur, or -N=C- (to form a quinoline or pyridine ring); or a pharmaceutically acceptable salt thereof.

The present invention provides also processes for their production and pharmaceutical compositions containing them as active ingredients.

Now, the present invention will be described with reference to the preferred embodiments.

Firstly, substituents R_1, R_2, X, Y, Z_1 and Z_2 in the compounds of the formula I of the present invention will be described. In the following definitions, "n" means normal, "i" means iso, "sec" means secondary and "t" means tertiary.

Specific Examples of R_1 include hydrogen, 2-propenyl, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Among them, preferred is hydrogen, ethyl or i-propyl. More preferred is hydrogen.

Specific examples of R_2 and R_3 include hydrogen, methyl, ethyl and n-propyl.

Specific examples of X includes chlorine and bromine.

Specific examples of Y include hydrogen, fluorine, chlorine, bromine, iodine, nitro, amino and $-AR_4$.

Here, specific examples of A include oxygen and sulfur.

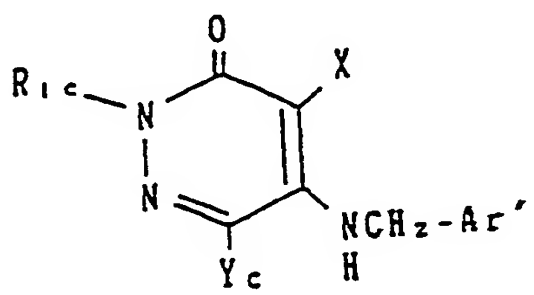
Specific examples of R_4 include hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, i-pentyl, sec-pentyl, n-hexyl, i-hexyl, sec-hexyl, n-heptyl, i-heptyl, sec-heptyl, n-octyl, i-octyl, sec-octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, benzyl, α-methylbenzyl,

α-ethylbenzyl, α-n-propylbenzyl and α-n-butylbenzyl.

Preferred specific examples of Y include hydrogen, nitro and -OR_4, wherein specific examples of R_4 include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, i-pentyl, sec-pentyl, n-hexyl, i-hexyl, sec-hexyl, n-heptyl, i-heptyl, sec-heptyl, n-octyl, i-octyl, sec-octyl, benzyl, α-methylbenzyl, α-ethylbenzyl, α-n-propylbenzyl and α-n-butylbenzyl.

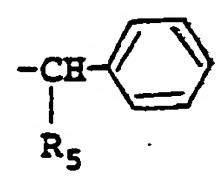
Specific examples of Ar include a naphthalene ring, a benzofuran ring, a benzothiophene ring, a furan ring, a thiophene ring, a quinoline ring and a pyridine ring to which Z_1 and Z_2 are bonded, wherein specific examples of Z_1 and Z_2 include, respectively, hydrogen, fluorine, chlorine, bromine, iodine, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy.

Among the compounds of the formula I of the present invention, preferred are a group of compounds represented by the formula:

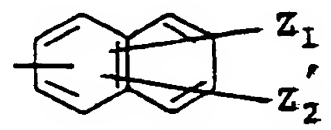


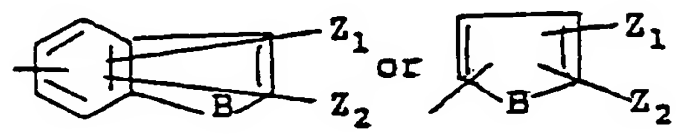
(IC)

wherein R_{1c} is hydrogen, ethyl; or i-propyl; X is chlorine, or bromine; Y_c is hydrogen, nitro, or -OR'_4 wherein R'_4 is straight chained, branched or cyclic C_1-C_8 alkyl, or



wherein R_5 is hydrogen, or straight chained or branched C_1-C_4 alkyl; and Ar' is





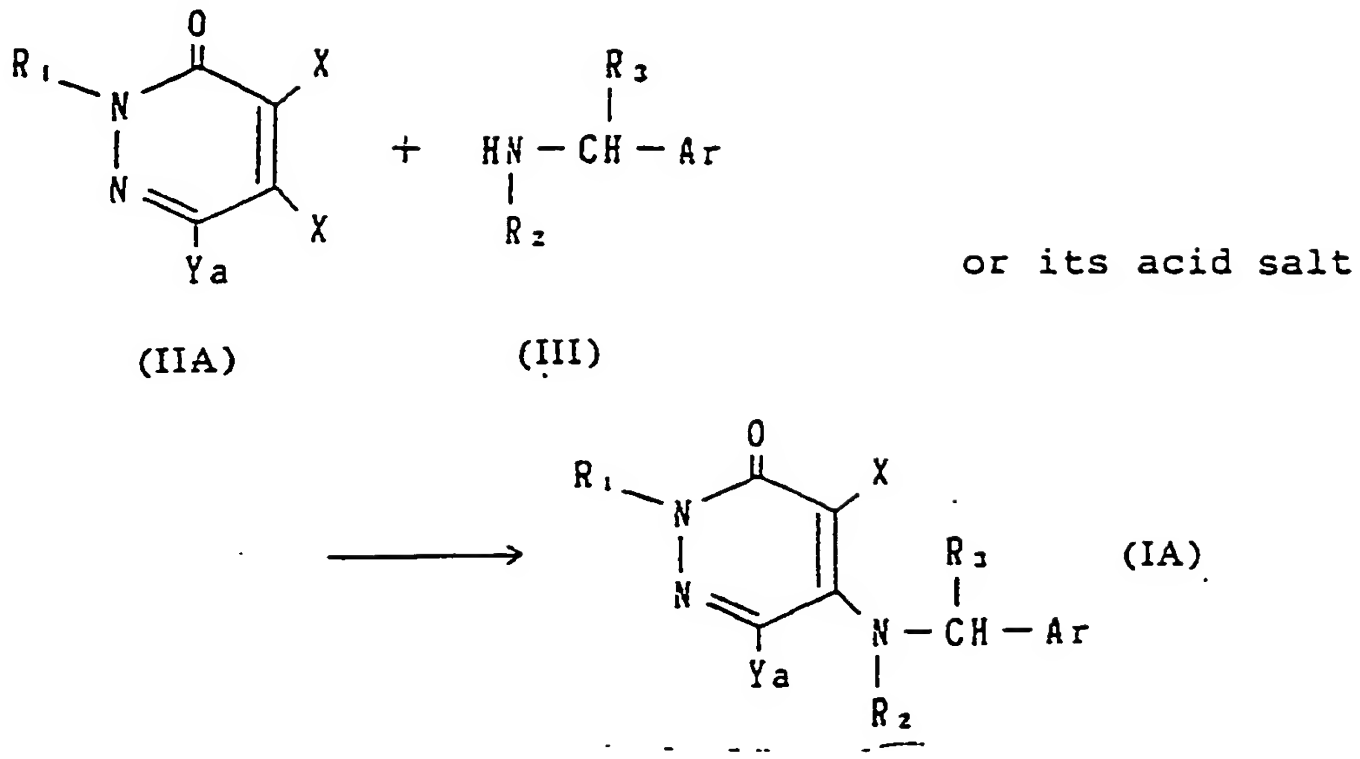
wherein each of Z_1 and Z_2 which may be the same or different, is hydrogen, halogen, straight or branched C_1-C_4 alkyl, or -OR_6 wherein R_6 is straight chained or branched C_1-C_4 alkyl, and B is oxygen, sulfur, or -N=C-.

The compound of the formula I of the present invention include optical isomers or stereo isomers based on from 1 to 3 asymmetric carbon atoms.

Now, the processes for producing the compounds of the present invention will be described.

3(2H)pyridazinones of the formula I and pharmaceutically acceptable salts thereof according to the present invention can be prepared by the following processes (1) to (5).

Process (1)



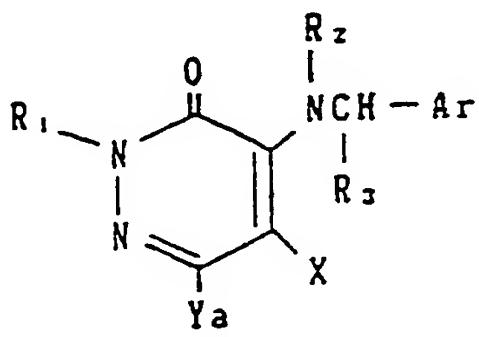
(IIA) (III) or its acid salt

(IA)

In the above formulas, Ya is hydrogen, halogen, nitro, amino or -OR_4, and R_1, R_2, R_3, R_4, X and Ar are as defined above.

Process (1) comprises reacting a 4,5-dihalo-3(2H)pyridazinone compound of the formula IIA with an arylmethylamine derivative of the formula III or its acid salt in an inert solvent, if necessary, in the presence of a dehydrohalogenating agent to obtain a compound of the formula IA, which has Ya at 6-position, among the compounds of the formula I of the present invention.

In Process (1), a compound of the formula VA:



(VA)

wherein Ya, R_1, R_2, R_3, X and Ar are as defined above, which is a position isomer of the compound of the formula IA having arylmethylamino at 4-position, is formed as a by-product.

The production ratios of the compounds IA and VA depend primarily upon the polarity of the solvent used. Namely, when a solvent of high polarity is used, the production ratio of the compound IA of the present invention tends to be high. Conversely, when a solvent of low polarity such as benzene, toluene or hexane is used, the production ratio of the compound VA tends to be high. Therefore, as a suitable solvent for efficient production of the compound IA of the present invention, an ether solvent such as tetrahydrofuran or 1,4-dioxane, an amide solvent such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide or N-methylpyrrolidone, acetonitrile, dimethylsulfoxide, an alcohol solvent such as methanol, ethanol or propanol, an organic amine solvent such as pyridine, triethylamine, N,N-dimethylaminoethanol or triethanolamine, or water, or a solvent mixture thereof, may be mentioned. The desired compound of the formula IA of the present invention can readily be separated and purified from the mixture of the compounds of the formulas IA and VA by conventional methods known per se in organic synthesis, such as fractional recrystallization or various silica gel chromatography.

During the reaction, hydrogen chloride or hydrogen bromide is generated. It is usually possible to improve the yield by adding to the reaction system a dehydrohalogenating agent which traps such a hydrogen halide.

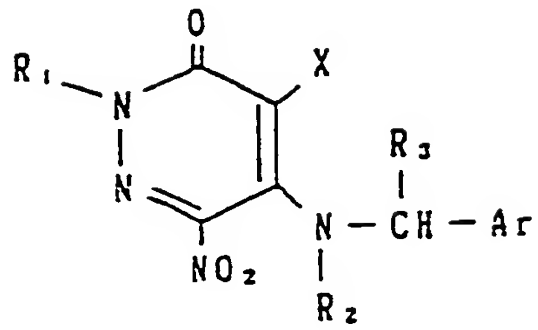
Any dehydrohalogenating agent may be used so long as it does not adversely affect the reaction and is capable of trapping a hydrogen halide. As such a dehydrohalogenating agent, an inorganic base such as potassium carbonate, sodium carbonate, potassium hydrogencarbonate, or sodium hydrogencarbonate, or an organic base such as N,N-dimethylaniline, N,N-diethylaniline, trimethylamine, triethylamine, N,N-diemthylaminoethanol or pyridine, may be mentioned. Otherwise, the starting material arylmethylamine derivative of the formula III may be used in an excessive amount as the dehydrohalogenating agent. This gives an improved yield in many cases. The reaction temperature may be within a range of from 10 °C to the boiling point of the solvent used for the reaction.

The molar ratio of the starting materials may optionally be set. However, the arylmethylamine derivative of the formula III or its salt may be used usually in an amount of from 1 to 10 moles, preferably from 1.2 to 5 moles, relative to one mole of the 4,5-dihalo-3(2H)pyridazinone derivative of the formula IIA.

The 4,5-dihalo-3(2H)pyridazinone derivative of the formula IIA can be prepared by a conventional process or by an application of a conventional organic reaction as described below. Namely, the compound of the formula IIA wherein Ya is hydrogen, can be prepared by the methods disclosed in the above-mentioned references (e) and (f). Compounds wherein Ya is other than hydrogen can be prepared by the method disclosed in reference (g). Further, among the arylmethylamine derivatives of the formula III and their salts in Process (1), those not available as commercial products can be prepared by the method disclosed in reference (e).

Process (2)

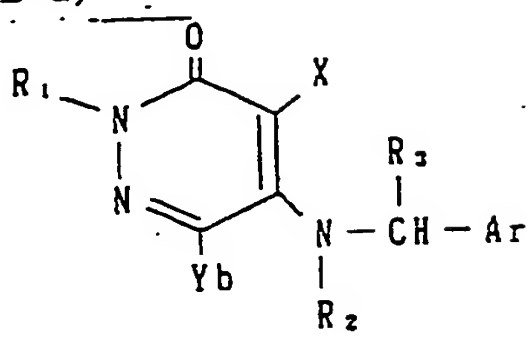
(i)



M⁺Yb⁻

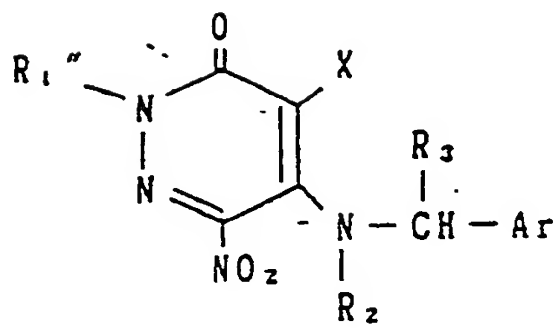
(IV)

(IB-a)



(IB)

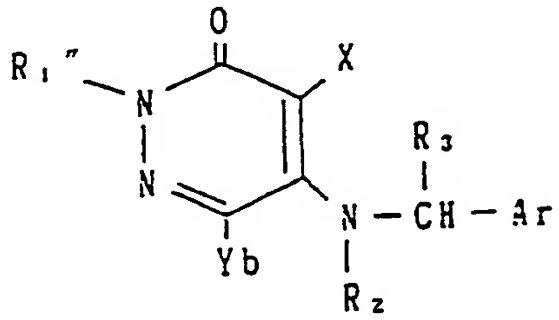
(ii)



M⁺Yb⁻

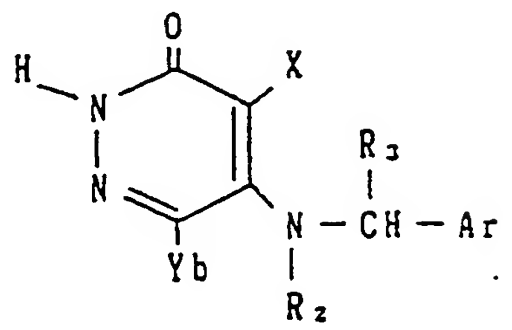
(IV)

(IB-b)



(IB-c)

Removal of the protective group



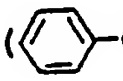
(IB')

In the above formulas, M is alkali metal, Yb is AR_4, R_1'' is a protective group, and R_1, R_2, R_3, R_4, X, Ar and A are as defined above.

Process (2) comprises a substitution reaction of nitro between a 6-nitro-5-arylmethylamino derivative of the formula IB-a or IB-b and an alkali metal salt of the formula IV to obtain a 6-substituted-5-arylmethylamino derivative of the formula IB or IB′ of the present invention.

Among the desired compounds, a compound having hydrogen at 2-position of pyridazinone, can be prepared by the direct route as shown in Process 2-(i), or by a route as shown in Process 2-(ii) which comprises converting the 6-nitro derivative of the formula IB-b protected at 2-position with R_1'' as a starting material to a compound of the formula IB-c and then removing the protecting group R_1'', to obtain the desired compound. The yield is usually better in the latter method in many cases.

As the protective group R_1'', tetrahydropyranyl, tetrahydrofuranyl, 2-trimethylsilylethoxymethyl (Me_3Si⌒OCH_2-), pivaloyloxymethyl(Me_3C-CO_2CH_2-),

benzyloxymethyl ( -CH_2OCH_2-),

methoxymethyl ($MeOCH_2$-) or CO_2R wherein R is lower alkyl, is preferably used. The removal of the protective group R_1'', can easily be conducted by a conventional method for the removal of such protective groups.

Here, the alkali metal of the formula M includes lithium, sodium and potassium.

Therefore, an alkali metal salt of the formula IV used as a nucleophilic agent includes an alkali metal hydroxide, a metal alkoxide, an alkali metal hydrosulfide and a metal mercaptide as defined by above R_4.

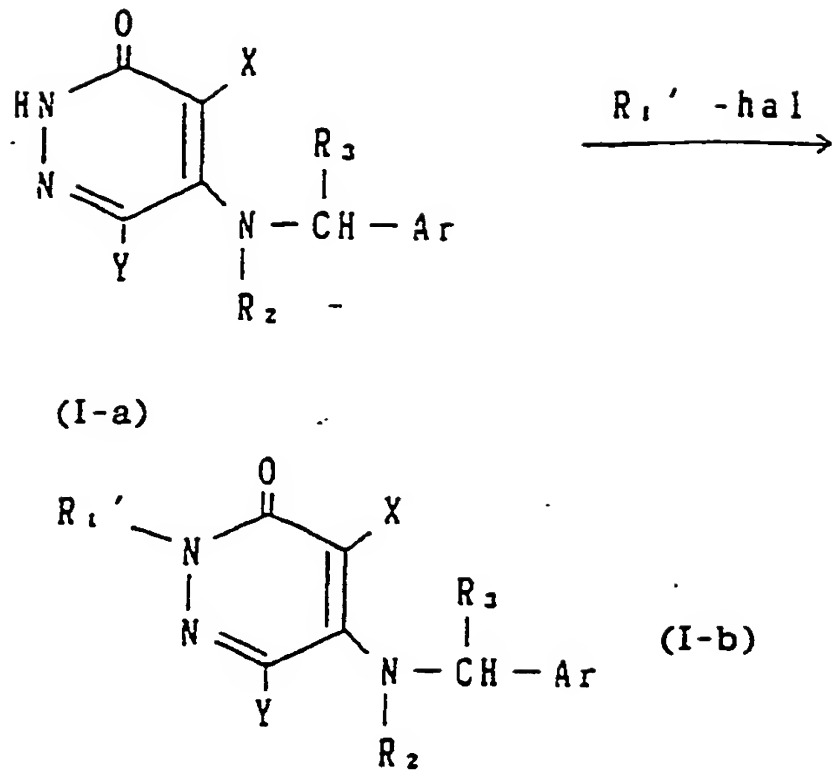
There is no particular restriction as to the reaction solvent so long as it is inert to the reaction, though it may be suitably selected depending upon the type of the alkali metal salt of the formula IV used for the reaction. In the case of using an alkali metal hydroxide or alkali metal hydrosulfide, the yield can often be improved by using an alcohol solvent such as methanol, ethanol, n-propanol or n-butanol, dimethylsulfoxide, an amide solvent such as formamide, N,N-dimethylformamide or N,N-dimethylaceteamide or a polar solvent such as water. In the case of using a metal alkoxide or metal mercaptide, the reaction is usually conducted in the corresponding alcohol or mercaptan. However, the reaction can be conducted in the above-mentioned ether solvent or in a medium including a benzene solvent such as benzene or toluene.

The reaction temperature varies depending upon the reactants used. It is usually within a range of from -15° C to the boiling point of the solvent used for the reaction.

The molar ratio of the starting materials can be optionally determined, and it is sufficient that the alkali metal salt of the formula IV is used in an amount of from 1.2 to 10 mols relative to one mol of the 6-nitro-5-arylmethylamino derivative of the formula IB-a or IB-b.

The desired compound can readily be isolated and purified by a method known per se in organic syntheses such as recrystallization, various silica gel chromatography or distillation.

Process (3)



(I-a)

(I-b)

In the above formulas, R_1' is 2-propenyl, or straight chained or branched C_1-C_4 alkyl, hal is chlorine, bromine, or iodine, and R_2, R_3, X, Y and Ar are as defined above.

Process (3) is a process which comprises reacting a compound of the formula I-a i.e. a compound of the formula I having hydrogen at 2-position of pyridazinone, with a halogeno derivative of the formula R_1'-hal, to obtain a 2-substituted compound of the formula I-b.

Process (3) is usually conducted in the presence of an inorganic base such as potassium carbonate, sodium carbonate, lithium carbonate, potassium hydrogencarbonate, sodium hydrogencarbonate or lithium hydroxide. Further, in the case where R_2 is alkyl in the formula I-a, it is possible to use a metal hydride such as sodium hydride or n-butyl lithium in addition to the above inorganic base.

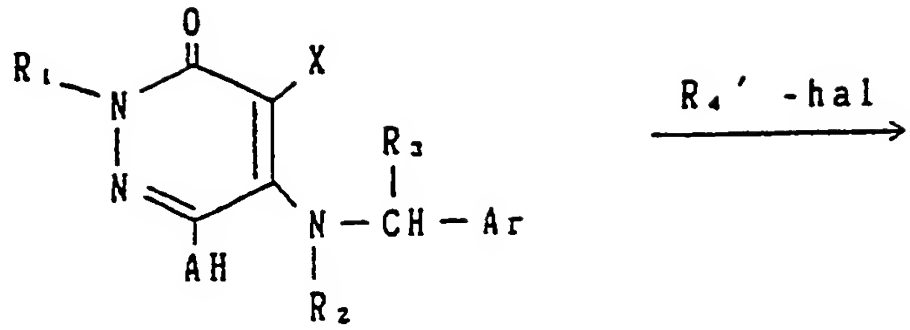
In the case of using the inorganic base, a ketone solvent such as acetone, methyl ethyl ketone or diethyl ketone, an amide solvent such as formamide, N,N-dimethylformamide or N,N-dimethylaceteamide, an alcohol solvent such as methanol or ethanol, or water, or a mixture thereof, is preferred as the reaction solvent, and in the case of using the metal hydride, an ether solvent is preferably used.

In the case of using the inorganic base, the reaction temperature is usually within a range of from 0 °C to the boiling point of the solvent, and in the case of using the metal hydride, it is usually within a range of from -78 to 60 °C.

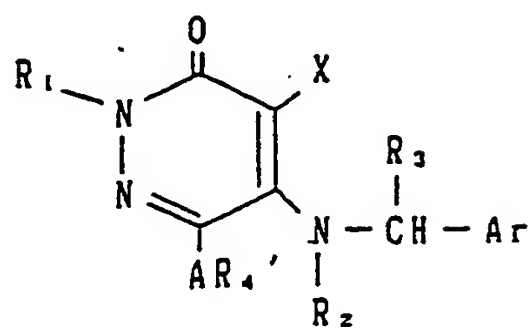
The molar ratio of the starting materials may optionally be determined. However, the halogen compound of the formula R_1-hal is used usually in an amount of from 1 to 5 mols relative to one mol of the compound of the formula I-a.

The desired compound can be isolated and purified in accordance with the method as described with respect to Process (2).

Process (4)



(IC-a)



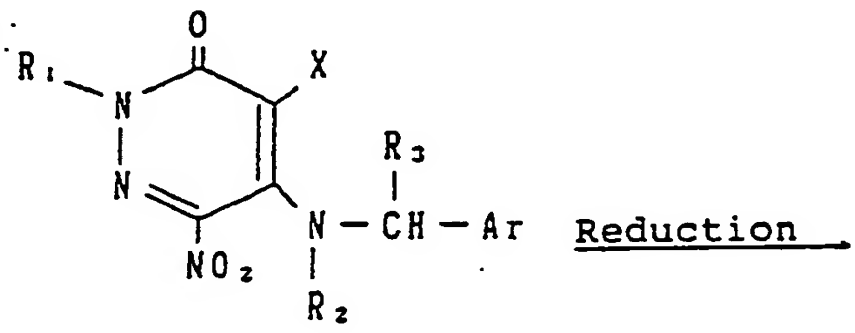
(IC-b)

In the above formulas, R_1, R_2, R_3, R_4', X, Ar and hal are as defined above.

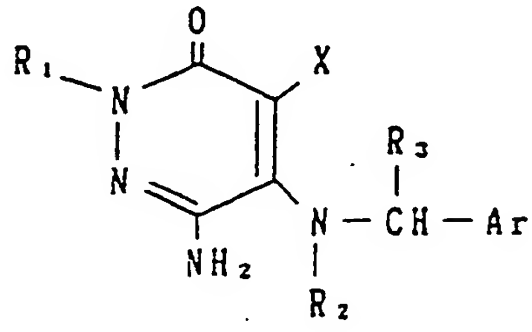
Process (4) is a process which comprises reacting a 6-hydroxy or 6-mercapto derivative of the formula IC-a with a halogeno derivative of the formula R_4'-hal, to obtain a 6-alkoxy or 6-substituted mercapto derivative of the formula IC-b of the present invention.

For process (4), it is possible to employ reaction conditions similar to those in the above Process (3).

Process (5)



(IB-a)



(ID)

In the above formulas, R_1, R_2, R_3, X and Ar are as defined above.

Process (5) is a process which comprises a reduction reaction of a 6-nitro derivative of the formula IB-a, to obtain a 6-amino derivative of the formula ID of the present invention.

For the reduction, a method of using sodium hydrosulfite, sodium sulfide or the like, or a method of using a metal such as iron, zinc, tin or the like in the presence of acid, may be employed. For this reduction reaction, it is desired to avoid a high temperature or a strong acidic condition with a high concentration of an acid, because a functional group such as halogen or arylmethyl, in the compound IB-a, will readily be reduced or eliminated under a strong acidic condition.

A protic solvent such as methanol, ethanol, n- propanol, acetic acid or water, or a mixture thereof, is usually preferably used as the solvent for the reaction. The reaction temperature may usually be within a range of from -10 to 50° C. The reaction usually proceeds smoothly.

As the manner of administration of the 3(2H)pyridazinones of the formula I or their pharmaceutically acceptable salts of the present invention, there may be mentioned a non-oral administration by injection (subcutaneous, intravenous, intramuscular or intraperitoneal injection), an ointment, a suppository or an aerosol, or an oral administration in the form of tablets, capsules, granules, pills, syrups, liquids, emulsions or suspension.

The above pharmacological or veterinary composition contains a compound of the present invention in an amount of from about 0.1 to about 99.5% by weight, based on the total weight of the composition. To the compound of the present invention or to the composition containing the compound of the present invention, other pharmacologically or veterinarily active compounds may be incorporated. Further, the composition of the present invention may contain a plurality of compounds of the present invention.

The clinical dose of the compound of the present invention varies depending upon the age, the body weight, the sensitivity or the symptom, etc. of the patient. However, the effective daily dose is usually from 0.003 to 1.5 g, preferably from 0.01 to 0.6 g, for an adult. However, if necessary, an amount outside the above range may be employed.

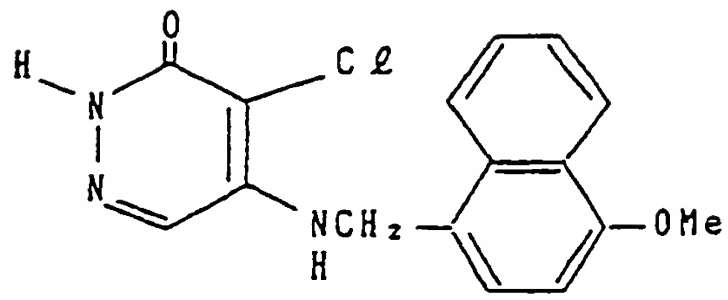
The compounds of the present invention may be formulated into various suitable formulations depending upon the manner of administration, in accordance with conventional methods commonly employed for the preparation of pharmaceutical formulations.

Namely, tablets, capsules, granules or pills for oral administration, may be prepared by using an excipient such as sugar, lactose, glucose, starch or mannitol; a binder such as syrups, gum arabic, gelatin, sorbitol, tragacant gum, methyl cellulose or polyvinylpyrrolidone; a disintegrant such as starch, carboxymethyl cellulose or its calcium salt, crystal cellulose powder or polyethylene glycol; a gloss agent such as talc, magnesium or calcium stearate or colloidal silica; or a lubricant such as sodium laurate or glycerol. The injections, solutions, emulsions, suspensions, syrups or aerosols, may be prepared by using a solvent for the active ingredient such as water, ethyl alcohol, isopropyl alcohol, propylene glycol, 1,3-butylene glycol, or polyethylene glycol; a surfactant such as a sorbitol fatty acid ester, a polyoxyethylene fatty acid ester, a polyoxyethylene ether of hydrogenated caster oil or lecithin; a suspending agent such as a sodium salt of carboxymethyl cellulose, a cellulose derivative such as methyl cellulose, or a natural rubber such as tragacant gum or gum arabic; or a preservative such as a paraoxy benzoic acid ester, benzalkonium chloride or a salt of sorbic acid. Likewise, the supporsitories may be prepared by using e.g. polyethylene glycol, lanolin or coconut butter.

Now, the present invention will be described in detail with reference to Examples including Preparation Examples, Formulation Examples and Test Examples. However, it should be understood that the present invention is by no means restricted by these specific Examples. In Preparation Examples or in Table 5, the symbols "NMR", "IR" and "MS" indicate "nuclear magnetic resonance spectrum", "infrared spectrum" and "mass spectrometry", respectively. IR was measured by the potassium bromide disk method, and NMR was measured in heavy chloroform, unless otherwise specified. In the MS data in Table 1, only the principal peaks or typical fragment peaks are given.

PREPARATION EXAMPLE 1

4-Chloro-5-(4-methoxy-1-naphthylmethylamino)-3(2H)pyridazinone (Compound No. 5)

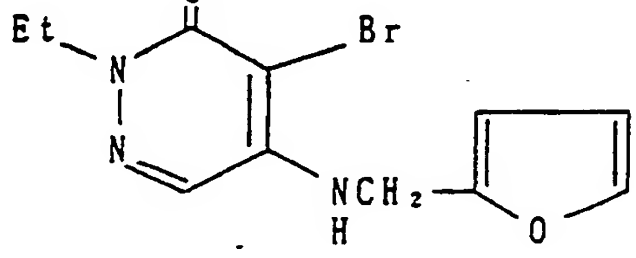


A mixture comprising 330 mg of 4,5-dichloro-3(2H)pyridazinone, 1.12 g of 4-methoxy-1-naphthylmethylamine and 30 ml of ethanol, was refluxed under stirring overnight. The solvent was evaporated under reduced pressure, and a mixture of ethyl acetate and ethyl ether was poured to the residue, whereupon precipitated crystals were collected by filtration. The product was recrystallized from a mixture of methanol/water to obtain 410 mg of the above identified compound as slightly yellow crystals having a melting point of from 265 to 266 °C.

NMR($CDCl_3$ + DMSO-d_6)
σ:8.2-7.2(5H,m),7.55(1H,s),
7.0-6.4(1H,broad s),6.77(1H,d), 4.9 0 (2H,d),3.95(3H,s).
MS(m/e) :314(M^+),280,171(100%)

PREPARATION EXAMPLE 2

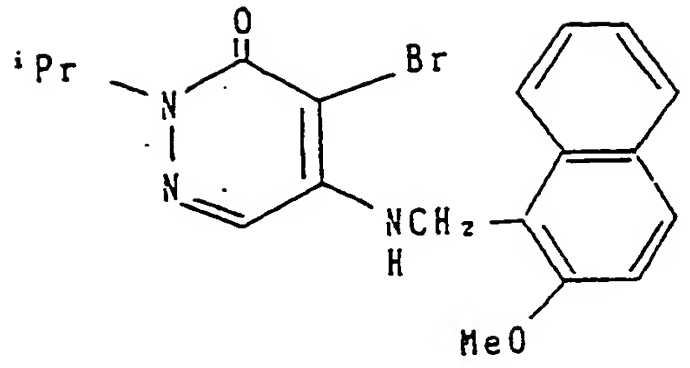
2-Ethyl-4-bromo-5-(2-furanylmethylamino)-3(2H)pyridazinone (Compound No. 22)



A mixture comprising 564 mg of 2-ethyl-4,5-dibromo-3(2H)pyridazinone, 291 mg of 2-furanylmethylamine, 530 mg of sodium carbonate, 15 ml of water and 15 ml of 1,4-dioxane, was refluxed under stirring for 5 hours. The solvent was distilled off under reduced pressure, and water was poured to the residue thus obtained. The mixture was extracted with ethyl acetate. The extract was washed with water and dried over sodium sulfate. Then, the solvent was distilled off. The residual oily substance thus obtained was purified by silica gel column chromatography by using a mixture of benzene/ethyl acetate (volume ratio of 2/1) as developer to obtain 294 mg of the above identified compound as colorless crystals having a melting point of from 120 to 123 °C (as recrystallized from a mixture of ethyl acetate/ethyl ether/n-hexane).
NMR
σ:7.51(1H,s),7.32(1H,d),6.35-6.15(2H,m), 5.3-4.9(1H,broad s)14.45(2H,d), 4.14(2H,q),1.33(3H,t).
MS(m/e):297(M^+),218,190,81(100%)

PREPARATION EXAMPLE 3

2-i-propyl-4-bromo-5-(2-methoxy-1-naphthylmethylamino)-3(2H)pyridazinone (Compound No. 26)



A mixture comprising 1.48 g of 2-i-propyl-4,5-dibromo-3(2H)pyridazinone, 1.68 g of 2-methoxy-1-naphthylmethylamine hydrochloride, 1.33 g of sodium carbonate, 30 ml of water and 30 ml of 1,4-dioxane, was refluxed under stirring overnight. Then, the solvent was distilled off under reduced pressure, and water was poured to the residue thus obtained. The mixture was extracted with ethyl acetate. The extract was washed sequentially with a 2 wt% hydrochloric acid aqueous solution, water and a saturated sodium chloride aqueous solution and then dried over sodium sulfate. Then, the solvent was distilled off. The residual solid thus obtained was crystallized from ethyl acetate/n-hexane to obtain 1.18 g of the above identified compound as colorless crystals having a melting point of from 160 to 161 °C.

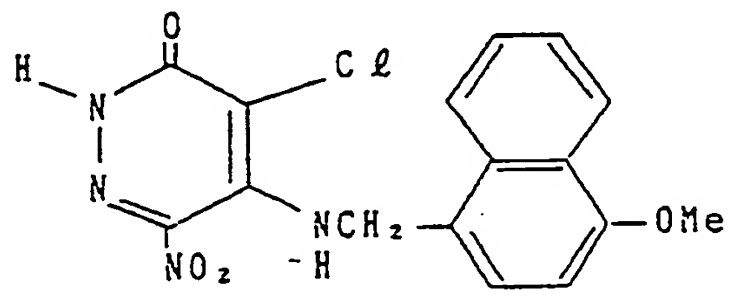
NMR

σ:8.1-71.(7H,m),5.6-4.8(2H,m),4.95(2H,d), 3.98(3H,s),1.30(6H,d).

MS(m/e) :401(M^+),322,171(100%),141.

PREPARATION EXAMPLE 4

4-Chloro-5-(4-methoxy-1-naphthylmethylamino)-6-nitro-3(2H)pyridazinone (Compound No. 30)



A mixture comprising 1.00 g of 4,5-dichloro-6-nitro-3(2H)pyridazinone, 2.67 g of 4-methoxy-1-naphthylamino and 50 ml of ethanol, was refluxed under stirring overnight. After cooling, precipitated crystals were collected by filtration. The product was dissolved in ethyl acetate, treated by silica gel and then recrystallized from ethyl acetate/ethyl ether to obtain 1.08 g of the above identified compound as yellowish orange crystals having a melting point of from 218 to 220 °C.

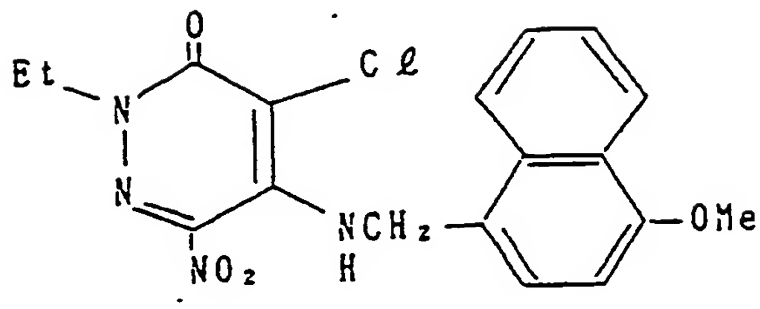
NMR($CDCl_3$ + DMSO-d_6)

σ:8.4-7.2(5H,m),7.2-6.7(1H,broad s), 6.74(1H,d),5.06(2H,d),3.93(3H,s).

MS(m/e) :360(M^+),325,171(100%).

PREPARATION EXAMPLE 5

2-Ethyl-4-chloro-5-(4-methoxy-1-naphthylmethylamino)-6-nitro-3(2H)pyridazinone (Compound No. 37)



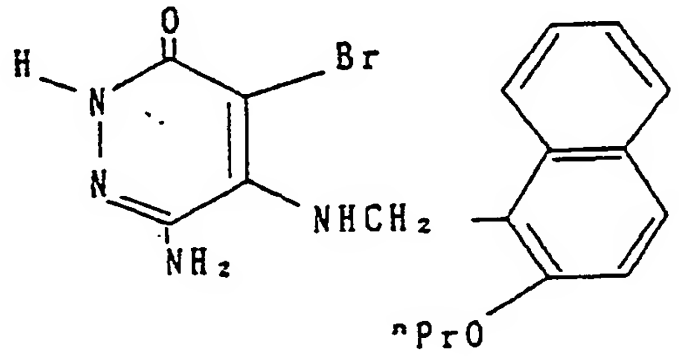
A mixture comprising 100 mg of 4-chloro-5-(4-methoxy-1-naphthylmethylamino)-6-nitro-3(2H)-pyridazinone (Compound No. 30) prepared in Preparation Example 4, 218 mg of ethyl iodide, 193 mg of potassium carbonate and 30 ml of methyl ethyl ketone, was refluxed under stirring for 1.5 hours. The reaction mixture was filtered, and the solvent of the filtrate was distilled off under reduced pressure. Water was poured to the residue thus obtained, and the mixture was extracted with benzene. The extract was washed with water and with a saturated sodium chloride aqueous solution and dried over sodium sulfate. Then, the solvent was distilled off to obtain 110 mg of the above identified compound as a slightly yellow brown caramel substance.

NMR

σ:8.9-7.1(5H,m),6.7-6.3(1H,broad s),
6.66(1H,d),5.03(2H,d),4.17(2H,q), 3.93(3H,s),1.38(3H,t).
MS(m/e):388(M^+),353,171(100%).

PREPARATION EXAMPLE 6

4-Bromo-5-(2-n-propoxy-1-naphthylmethylamino)-6-amino-3(2H)pyridazinone (Compound No. 46)

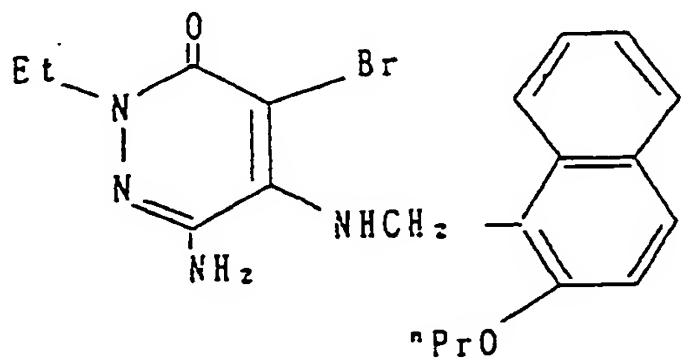


500 mg of 4-bromo-5-(2-n-propoxy-1-naphthylmethylamino)-6-nitro-3(2H)pyridazinone (Compound No. 45) was dissolved in a mixture comprising 50 ml of ethanol and 25 ml of a 10% sodium carbonate aqueous solution. Then, 1.40 g of sodium hydrosulfite was gradually added under stirring, and the mixture was stirred at room temperature for 1 hour and then the reaction solution was left to stand overnight. Glacial acetic acid was dropwise added to neutralize the reaction solution. Then, the solvent was distilled off under reduced pressure. Water was poured to the residue thus obtained, and the mixture was extracted with chloroform. The extract was washed sequentially with water and with a saturated sodium chloride aqueous solution and then dried over sodium sulfate. The solvent was distilled off to obtain a yellowish orange solid substance. This product was purified by silica gel column chromatography by using chloroform and a mixture of chloroform/methanol (volume ratio of 20/1) as developers to obtain 160 mg of the above identified compound as colorless crystals having a melting point of from 199 to 203° C (as recrystallized from chloroform/ethyl ether) from the fraction eluted with the mixture of chloroform/methanol (volume ratio of 20/1).

NMR($CDCl_3$ + DMSO-d_6)
σ:8.1-7.1(6H,m),5.12(2H,d) ,4.07(2H,t), 1.02(3H,t).
MS(m/e):402(M^+),323,199(100%),157.

PREPARATION EXAMPLE 7

2-Ethyl-4-bromo-5-(2-n-propoxy-1-naphthylmethylamino)-6-amino-3(2H)pyridazinone (Compound No. 49)



i) A mixture comprising 50 mg of 4-bromo-5-(2-n-propoxy-1-naphthylmethylamino)-6-amino-3(2H)-pyridazinone 2,5 (Compound No. 46) prepared in Preparation Example 6, 94 mg of ethyl iodide, 83 mg of potassium carbonate, 20 ml of methyl ethyl ketone and 1 ml of N,N-dimethylformamide, was refluxed under stirring for 1.5 hours. Then, the solvent was distilled off under reduced pressure, and water was poured to the residue thus obtained. The mixture was extracted with benzene. The extract was washed with water and with a saturated sodium chloride aqueous solution and then dried over sodium sulfate. Then, the solvent was distilled off. The residual solid substance was purified by silica gel column chromatography by using chloroform and a mixture of chloroform/methanol (volume ratio of 10/1) as developers, to obtain 15 mg of the above identified compound as colorless crystals having a melting point of from 144 to 145°C (as recrystallized from chloroform/ethyl ether/hexane).

NMR

σ:8.0-7.1(6H,m),4.94(2H,d),4.31(2H,broad s), 4.13(2H,q),3.95(2H,t),1.27,1.06 (each 3H,t).

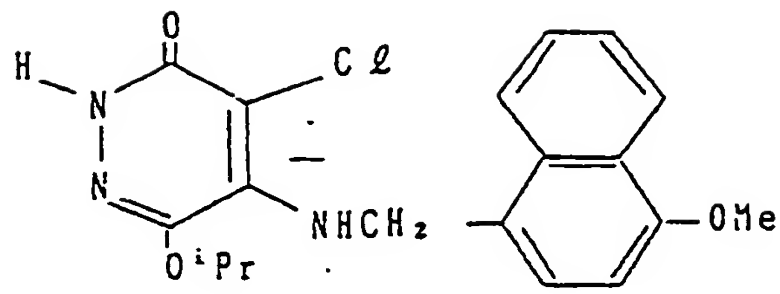
MS(m/e) :430(M^+),351,199(100%) ,157,129.

IR(ν_{max}^{KBr}) cm^{-1} 3340,3210,1620 (shoulder), 1600,1515,1420.

ii) 530 mg of 2-ethyl-4-bromo-5-(2-n-propoxy-1-naphthylmethylamino)-6-nitro-3(2H)pyridazinone (Compound No. 48) was dissolved in a mixture comprising 50 ml of ethanol and 25 ml of a 10 wt% sodium carbonate aqueous solution. Then, 1.0 g of sodium hydrosulfite was gradually added under stirring, and the mixture was then stirred at room temperature for 2.5 hours. Glacial acetic acid was added to neutralize the reaction solution. Then, the solvent was distilled off under reduced pressure. Water was poured to the residue thus obtained, and the mixture was extracted with chloroform. The extract was washed sequentially with water and with a saturated sodium chloride aqueous solution and then dried over sodium sulfate. Then, the solvent was distilled off to obtain a residual yellowish orange solid substance. This product was purified by silica gel column chromatography by using chloroform and a mixture of chloroform/methanol (volume ratio of 10/1) as developers to obtain 10 mg of colorless crystals. This product was found to show the same behavior on the silica gel thin layer chromatography as the substance obtained in the above method i), and was identical with it also in NMR, MS and IR spectrum.

PREPARATION EXAMPLE 8

4-Chloro-5-(4-methoxy-1-naphthylmethylamino)-6-i-propoxy-3(2H)pyridazinone (Compound No. 32)

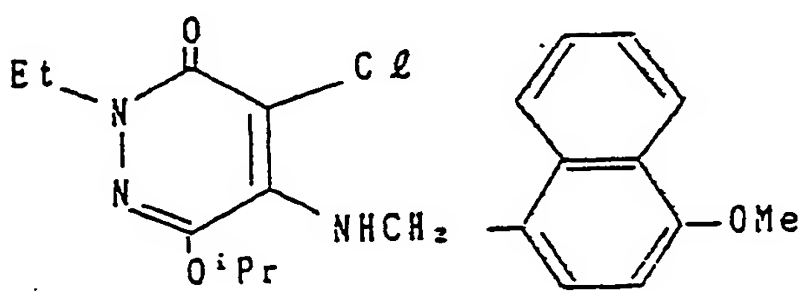


A mixture comprising 350 mg of 4,5-dichloro-6-i-propoxy-3(2H)pyridazinone 1.23 g of 4-methoxy-1-naphthylmethylamine and 30 ml of a mixture of water/1, 4-dioxane (volume ratio of 1/1), was refluxed under stirring for 3.5 hours. The reaction mixture was concentrated, and precipitated crystals were collected by filtration and recrystallized from a mixture of methanol/water to obtain 420 mg of the above identified compound as colorless crystals having a melting point of from 244 to 247° C.

NMR($CDCl_3$-DMSO-d_6)
σ:8.4-7.2(5H,m),6.67(1H,d),5.70(1H,broad s), 5.17(2H,d) ,3.95(3H,s),1.12(6H,d).
MS(m/e):373(M^*),338,171(100%).

PREPARATION EXAMPLE 9

2-Ethyl-4-chloro-5-(4-methoxy-1-naphthylmethylamino-6-i-propoxy-3(2H)pyridazinone (Compound No. 40)



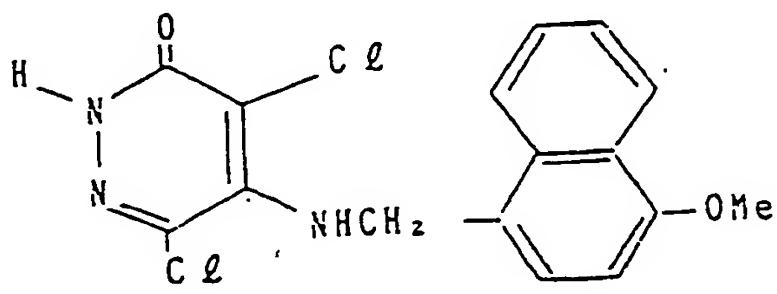
i) A mixture comprising 150 mg of 4-chloro-5-(4-methoxy-1-naphthylmethylamino)-6-i-propoxy-3(2H)-pyridazinone prepared in Preparation Example 8, 310 mg of ethyl iodide, 280 mg of potassium carbonate, 30 ml of methyl ethyl ketone, and 2 ml of N,N- dimethylformamide, was refluxed under stirring for 1.5 hours. The reaction mixture was filtered, and the solvent of the filtrate was distilled off under reduced pressure. Water was poured to the residue thus obtained, and the mixture was extracted with benzene. The extract was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. Then, the solvent was distilled off. The residual oily substance thus obtained was purified by silica gel column chromatography. Elution was conducted with a mixture of benzene/ethyl acetate (volume ratio of 3/1), and crystallization was further conducted from ethyl ether/n-hexane to obtain 110 mg of the above identified compound as colorless crystals with a melting point of from 118.5 to 120° C.

NMR
σ:8.5-7.2(5H,m),6.65(1H,d),5.12(2H,d), 4.01(2H,q),3.90(3H,s),1.29(3H,t), 1.18(6H,d).
MS(m/e):401(M^*),366.171(100%).

ii) 150 mg of 2-ethyl-4-chloro-5-(4-methoxy-1-naphthylamino)-6-nitro-3(2H)pyridazinone (Compound No. 37) prepared in Preparation Example 5 was dissolved in 5 ml of i-propanol. While stirring the solution, a solution having 30 mg of sodium dissolved in 5 ml of i-propanol under heating, was dropwise added. After the dropwise addition, the reaction mixture was stirred at room temperature overnight. Water was poured to the reaction solution, and the mixture was extracted with chloroform. The extract was washed sequentially with water and a saturated sodium chloride aqueous solution and then dried over sodium sulfate. Then, the solvent was distilled off. The residual oily substance thus obtained was purified by silica gel column chromatography (developer: benzene/ethyl acetate = 5-3/1) to obtain 20 mg of the above identified compound. The behavior on a silica gel thin layer chromatography and NMR and MS spectrum data of this product were identical with those of the product obtained in the above method i).

PREPARATION EXAMPLE 10

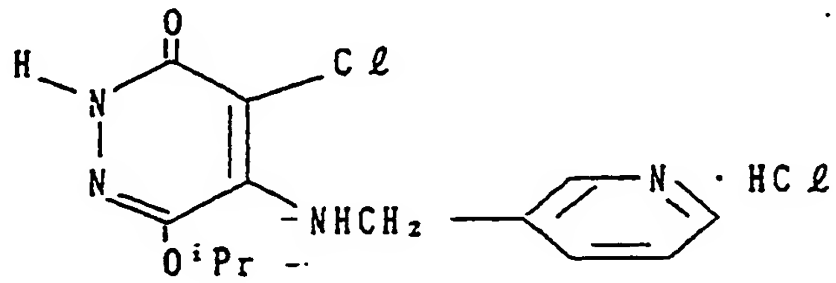
4,6-Dichloro-5-(4-methoxy-1-naphthylmethylamino)-3(2H)pyridazinone (Compound No. 34)



A mixture comprising 800 mg of 4,5,6-trichloro-3(2H)pyridazinone, 2.68 g of 4-methoxy-1-naphthylmethylamine and 10 ml of ethanol, was refluxed under stirring for 4 hours. After cooling, precipitated crystals were collected by filtration. Then, the product was dissolved in hot ethyl acetate and treated by silica gel. The filtrate was concentrated, and precipitated crystals were collected by filtration to obtain 330 mg of the above identified compound as colorless crystals having a melting point of from 228 to 231 °C.
NMR($CDCl_3$ + DMSO-d_6)
σ:8.4-7.2(5H,m),6.72(1H,d),5.18(2H,d), 3.95(3H,s)
MS(m/e) :349(M^+),314,171(100%).

PREPARATION EXAMPLE 11

4-Chloro-5-(3-pyridylmethylamino)-6-i-propoxy-3(2H)pyridazinone hydrochloride (Compound No. 51)



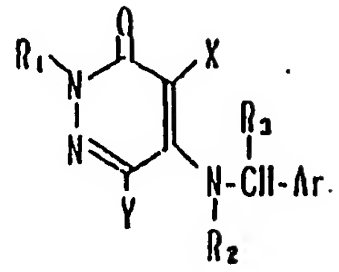
2.32 g of 4-chloro-5-(3-pyridylmethylamino)-6-i-propoxy-3(2H)pyridazinone prepared in the same manner as in Preparation Example 8, was dissolved in a 10% hydrogen chloride methanol solution, and the solution was stirred at room temperature for 1.5 hours. The solvent was distilled off under reduced pressure, and the obtained residue was crystallized from methanol/diethyl ether, to obtain 2.55 g of the above identified compound as colorless crystals having a melting point of from 232 to 234 °C.
Ms(m/e):294(M^+-HCl),252(100%),217,92.

Compounds prepared in the synthetic manner similar to those in the above Preparation Examples are shown in Table 1. In the right hand end column in the Table, the number of the Example employed is indicated.

Further, 3(2H)pyridazinones of the formula I and their pharmaceutically acceptable salts of the present invention include compounds listed in Table II in addition to those described in the above Preparation Examples and in Table I.

In Tables I and II, n means "normal", i means "iso", sec means "secondary", Me means "a methyl group", Et means "an ethyl group", Pr means "a propyl group", Bu menas "a butyl group", Pen means "a pentyl group", Hex means "a hexyl group", Hep means "a heptyl group", Oct means "an octyl group", and Ph means "a phenyl group".

Table I



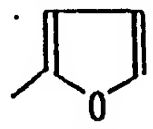
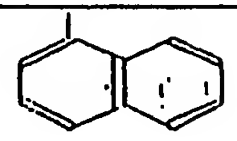
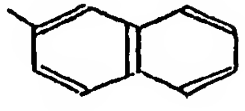
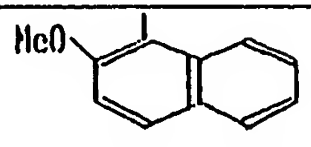
Compound No.	R_1	R_2	R_3	X	Y	Ar	m.p. (°C)	MS(m/e)	Example No.
1	H	H	H	Cℓ	H		170~172	225(M⁺), 81(100%)	1
2	H	H	H	Cℓ	H		233~235	285(M⁺), 141(100%)	1
3	H	H	H	Cℓ	H		249~252	285(M⁺), 141(100%)	1
4	H	H	H	Cℓ	H		248~252	315(M⁺), 171(100%)	1

Table I (continued)

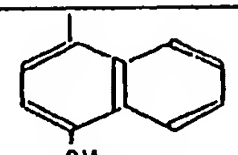
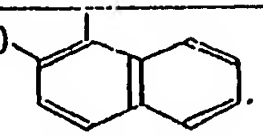
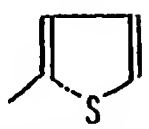
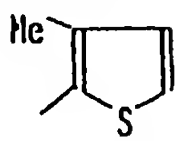
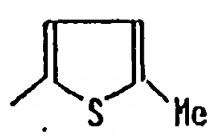
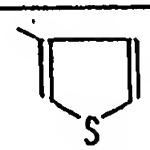
Compound No.	R_1	R_2	R_3	X	Y	Ar	m.p. (°C)	MS(m/e)	Example No.
5	H	H	H	Cℓ	H		265~266	See Preparation Example 1	1
6	H	H	H	Cℓ	H		215~217	343(M⁺), 157(100%)	1
7	H	H	H	Cℓ	H		208~210	241(M⁺), 97(100%)	1
8	H	H	H	Cℓ	H		203~205	255(M⁺), 111(100%)	1
9	H	H	H	Cℓ	H		174~175	255(M⁺), 111(100%)	1
10	H	H	H	Cℓ	H		230~235	241(M⁺), 97(100%)	1

Table I (continued)

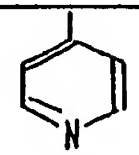
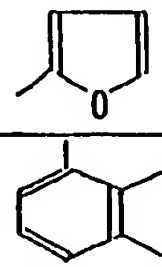
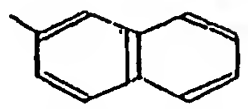
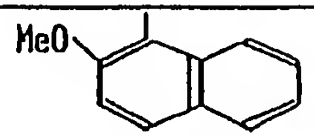
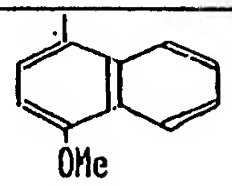
Compound No.	R_1	R_2	R_3	X	Y	Ar	m.p. (°C)	MS(m/e)	Example No.
11	H	H	H	Cℓ	H		252~256	236(M⁺), 92(100%)	1
12	H	H	H	Br	H		162~165	269(M⁺), 81(100%)	1
13	H	H	H	Br	H		258~262	329(M⁺), 141(100%)	1
14	H	H	H	Br	H		238~242	329(M⁺), 141(100%)	1
15	H	H	H	Br	H		210~214	359(M⁺), 171(100%)	1
16	H	H	H	Br	H		223~224	359(M⁺), 171(100%)	1

Table I (continued)

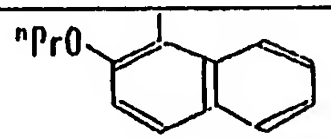
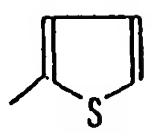
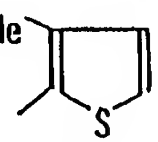
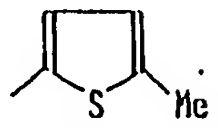
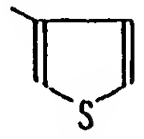
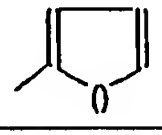
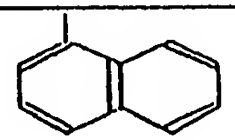
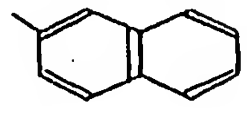
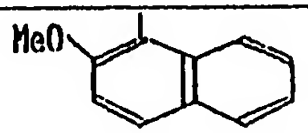
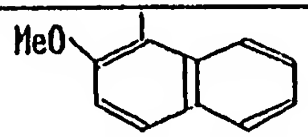
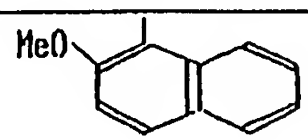
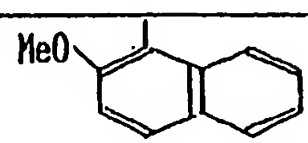
Compound No.	R_1	R_2	R_3	X	Y	Ar	m.p. (°C)	MS(m/e)	Example No.
17	H	H	H	Br	H		193~195	387(M+), 157(100%)	1
18	H	H	H	Br	H		203~205	285(M+), 97(100%)	1
19	H	H	H	Br	H		194~196	299(M+), 111(100%)	1
20	H	H	H	Br	H		176~178	299(M+), 111(100%)	1
21	H	H	H	Br	H		214~217	285(M+), 97(100%)	1
22	Et	H	H	Br	H		120~123	See Preparation Example 2	2

Table I (continued)

Compound No.	R_1	R_2	R_3	X	Y	Ar	m.p. (°C)	MS(m/e)	Example No.
23	Et	H	H	Br	H		251~255	357(M+),141(100%)	2
24	Et	H	H	Br	H		174~176	357(M+),141(100%)	3
25	Et	H	H	Br	H		168~170	387(M+),171(100%)	3
26	^{i}Pr	H	H	Br	H		160~161	See Preparation Example 3	3
27	H	Me	H	Cl	H		235~238	329(M+),171(100%)	1
28	H	Me	H	Br	H		212~214	294(M+-Br),171(100%)	1

EP 0 376 079 A1

Table I (continued)

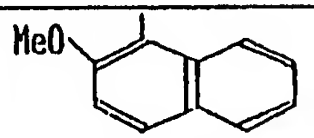
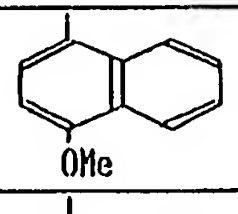
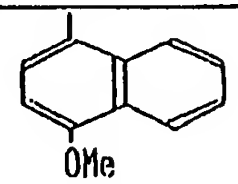
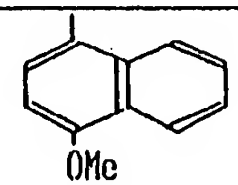
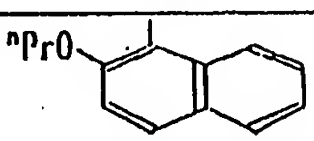
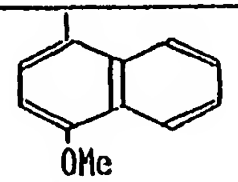
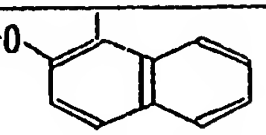
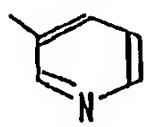
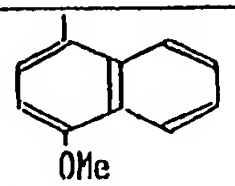
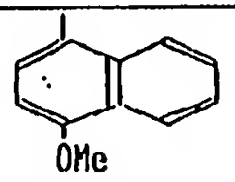
Compound No.	R_1	R_2	R_3	X	Y	Ar	m.p. (°C)	MS(m/e)	Example No.
29	H	Me	H	Cℓ	NO_2		203~205	374(M⁺), 171(100%)	1
30	H	H	H	Cℓ	NO_2		218~220	See Preparation Example 4	1
31	H	H	H	Cℓ	OEt		250~253	359(M⁺), 171(100%)	8
32	H	H	H	Cℓ	O^iPr		244~247	See Preparation Example 8	8
33	H	H	H	Cℓ	O^iPr		159~162	401(M⁺), 199(100%)	8

Table I (continued)

Compound No.	R_1	R_2	R_3	X	Y	Ar	m.p. (°C)	MS(m/e)	Example No.
34	H	H	H	Cℓ	Cℓ		228~231	See Preparation Example 10	10
35	H	H	H	Cℓ	Cℓ		179~198.5	377(M⁺), 199(100%)	10
36	H	H	H	Cℓ	O^iPr		237~240	294(M⁺), 92(100%)	8
37	Et	H	H	Cℓ	NO_2		Caramel-like	See Preparation Example 5	5
38	Et	H	H	Cℓ	OMe		135~137	373(M⁺), 171(100%)	9-ii)

EP 0 376 079 A1

Table I (continued)

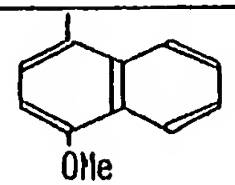
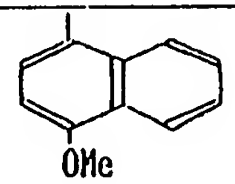
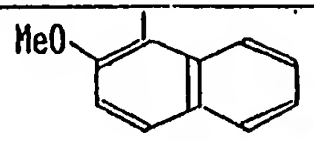
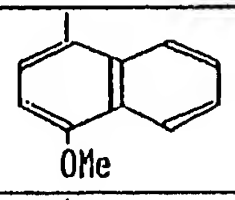
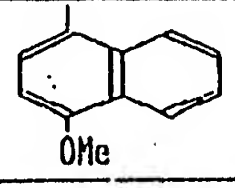
Compound No.	R_1	R_2	R_3	X	Y	Ar	m.p. (°C)	MS(m/e)	Example No.
39	Et	H	H	Cℓ	OEt		131.5~133.5	387(M⁺), 171(100%)	9-ii)
40	Et	H	H	Cℓ	O^{i}Pr		118~120	See Preparation Example 9	9
41	^{i}Pr	Me	H	Cℓ	NO_2		Oily	416(M⁺), 171(100%)	5
42	^{i}Pr	H	H	Cℓ	NO_2		147~148.5	402(M⁺), 171(100%)	5
43	^{i}Pr	H	H	Cℓ	O^{i}Pr		119~121	415(M⁺), 171(100%)	9-ii)

Table I (continued)

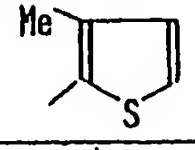
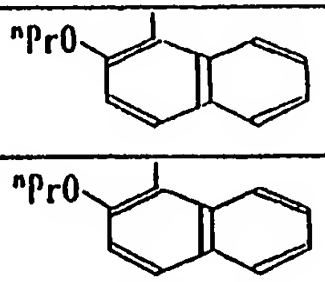
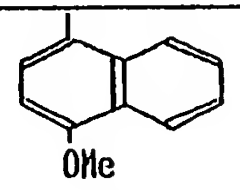
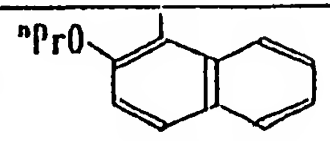
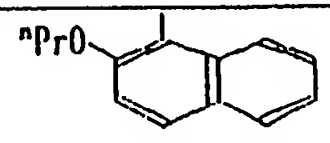
Compound No.	R_1	R_2	R_3	X	Y	Ar	m.p. (°C)	MS(m/e)	Example No.
44	H	H	H	Br	NO_2		128~134	344(M⁺), 111(100%)	1
45	H	H	H	Br	NO_2		175~178	432(M⁺), 199(100%)	1
46	H	H	H	Br	NH_2		199~203	See Preparation Example 6	6
47	H	H	H	Br	NO_2		212~215	404(M⁺), 171(100%)	1
48	Et	H	H	Br	NO_2		油状物	406(M⁺), 199(100%)	5
49	Et	H	H	Br	NH_2		144~145	See Preparation Example 7	7

Table I (continued)

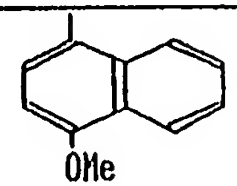
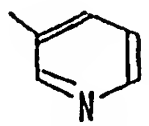
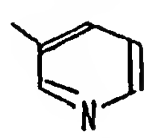
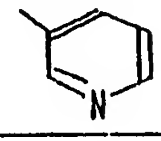
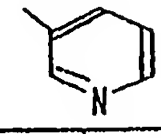
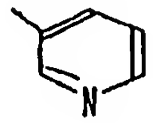
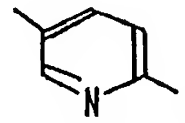
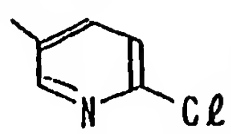
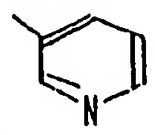
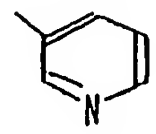
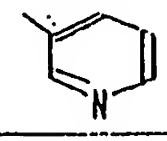
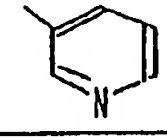
Compound No.	R_1	R_2	R_3	X	Y	Ar	m.p. (°C)	MS(m/e)	Example No.
50	Et	H	H	Br	NO_2		Oily	432(M⁺), 171 (100%)	5
51	H	H	H	Cℓ	O^iPr	 · HCℓ	232~234	See Preparation Example 11	11
52	H	H	H	Cℓ	H		255~257	236 (M⁺), 92(100%)	1
53	H	H	H	Cℓ	OEt		229~232	280 (M⁺), 92(100%)	8
54	H	H	H	Cℓ	O^nBu		159~160	308 (M⁺), 92(100%)	8

Table I (continued)

Compound No.	R_1	R_2	R_3	X	Y	Ar	m.p. (°C)	MS(m/e)	Example No.
55	H	H	H	Cℓ	O^{n}Bu	 · HCℓ	178~184	308 (M$^+$−HCℓ), 217 (100%)	11
56	H	H	H	Cℓ	O^{n}Bu		141~142	338 (M$^+$), 122 (100%)	8
57	H	H	H	Cℓ	O^{n}Bu		207~209	342 (M$^+$), 126 (100%)	8
58	H	H	H	Cℓ	O^{n}Pen		148~149.5	322 (M$^+$), 92 (100%)	8
59	H	H	H	Cℓ	O^{n}Pen	 · HCℓ	171~178	322 (M$^+$−HCℓ), 217 (100%)	11
60	H	H	H	Cℓ	O^{n}Hex		150~151.5	336 (M$^+$), 92 (100%)	8
61	H	H	H	Cℓ	O^{n}Hex	 · HCℓ	181~190	336 (M$^+$−HCℓ), 217 (100%)	11

EP 0 376 079 A1

Table I (continued)

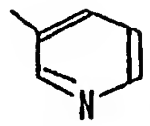
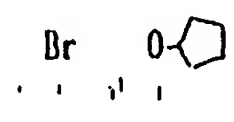
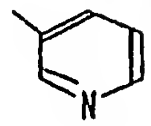
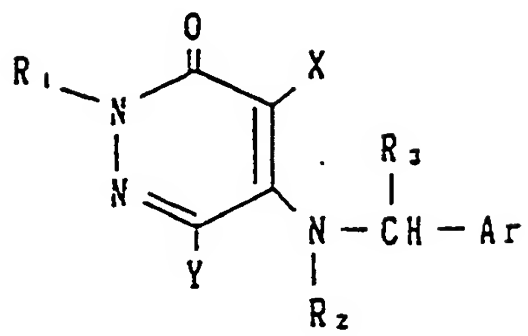
Compound No.	R_1	R_2	R_3	X	Y	Ar	m.p. (°C)	MS(m/e)	Example No.
62	H	H	H	Cℓ	OCH_2Ph	 · HCℓ	164~165	342 (M⁺), 251 (100%)	11
63	H	H	H	Br	O 		222~223	364 (M⁺), 92 (100%)	8

Table II



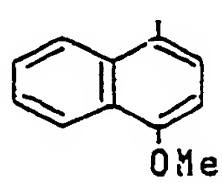
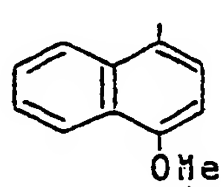
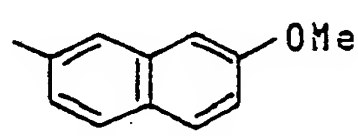
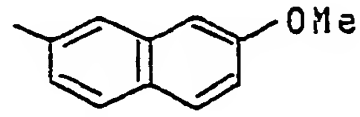
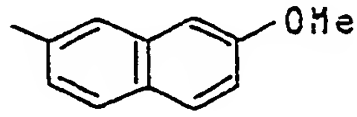
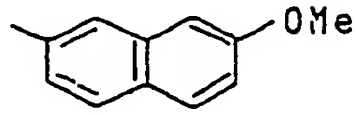
R_1	R_2	R_3	X	Y	Ar
H	H	H	Br	OEt	
H	H	H	Cℓ	OMe	
H	H	H	Cℓ	OEt	
H	H	H	Cℓ	O^iPr	
H	H	H	Br	O^iPr	
H	H	H	Cℓ	$O^{sec}Bu$	

Table II (continued)

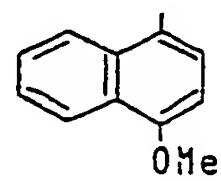
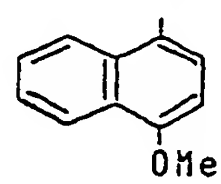
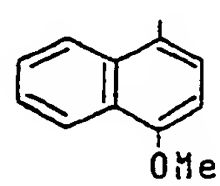
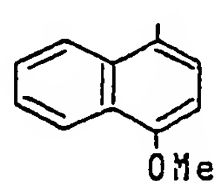
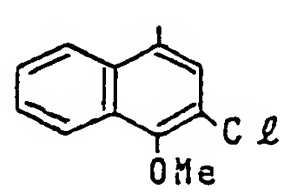
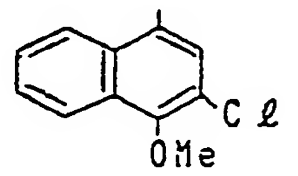
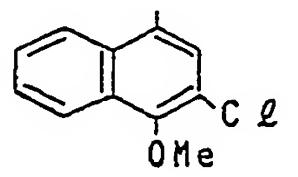
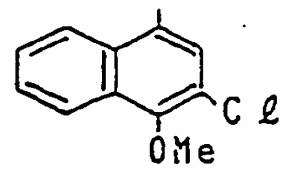
R_1	R_2	R_3	X	Y	Ar
H	H	H	Cℓ	O^{n}Bu	
H	H	H	Cℓ	O^{n}Hex	
H	H	H	Cℓ	O^{n}Hep	
H	H	H	Cℓ	^{n}Oct	
H	H	H	Cℓ	OEt	
H	H	H	Cℓ	O^{n}Pr	
H	H	H	Cℓ	O^{n}Bu	
H	H	H	Cℓ	OCHPh Me	

Table II (continued)

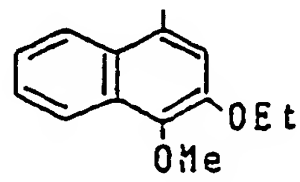
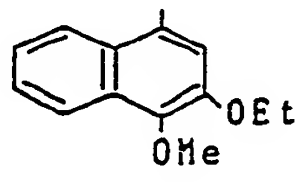
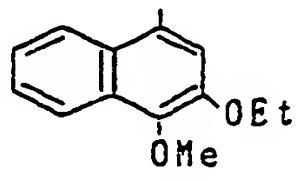
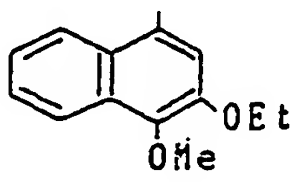
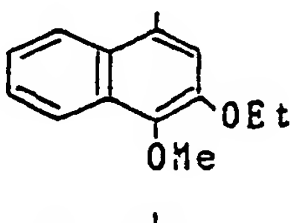
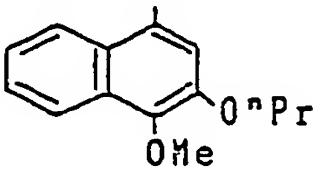
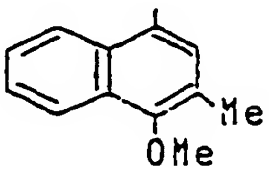
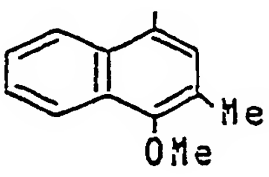
R_1	R_2	R_3	X	Y	Ar
H	H	H	Br	OEt	
H	H	H	Br	O^iPr	
H	H	H	Br	O^nBu	
H	H	H	Br	O-cyclopentyl	
H	H	H	Br	OCHPh(Me)	
H	H	H	Br	OMe	
H	H	H	Br	OEt	
H	H	H	Br	O^iPr	

Table II (continued)

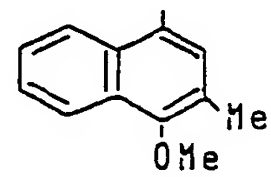
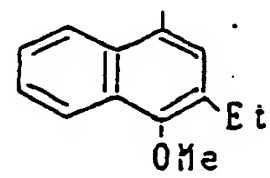
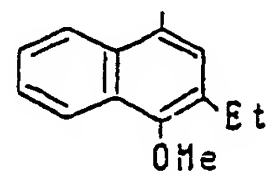
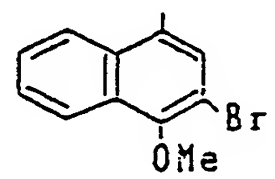
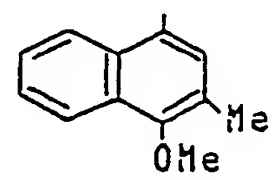
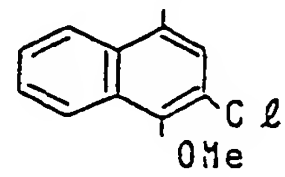
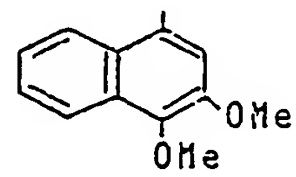
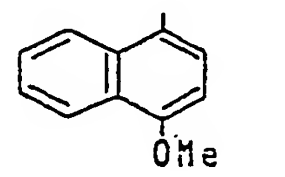
R_1	R_2	R_3	X	Y	Ar
H	H	H	Br	O^{n}Bu	
H	H	H	Cℓ	OMe	
H	H	H	Cℓ	OEt	
H	H	H	Br	SMe	
H	H	H	Br	SMe	
H	H	H	Br	S- 	
H	H	H	Br	SCHPh | Me	
H	H	H	Br	SEt	

Table II (continued)

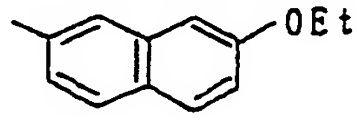
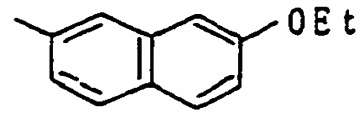
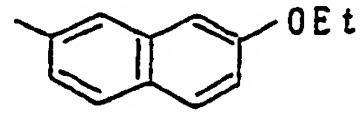
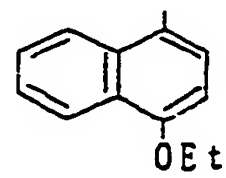
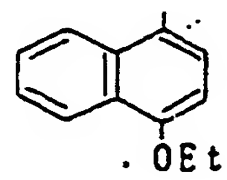
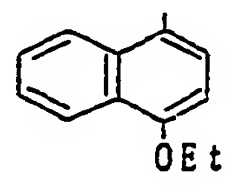
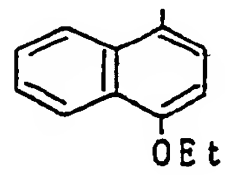
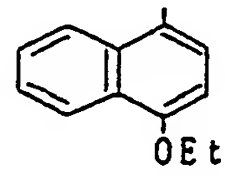
R_1	R_2	R_3	X	Y	Ar
H	H	H	Br	H	
Et	H	H	Cℓ	H	
H	H	Me	Br	H	
H	H	H	Cℓ	H	
H	H	H	Cℓ	OEt	
H	H	H	Br	O^iPr	
H	H	H	Cℓ	$O^{sec}Bu$	
H	H	H	Br	O^iBu	

Table II (continued)

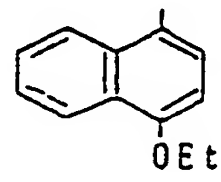
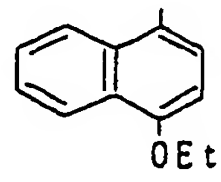
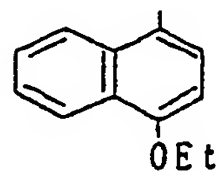
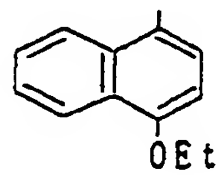
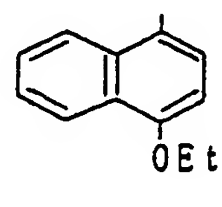
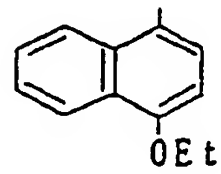
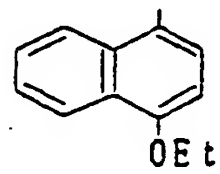
R_1	R_2	R_3	X	Y	Ar
H	H	H	Cℓ	SMe	
H	H	H	Br	SEt	
H	H	H	Cℓ	Cℓ	
H	H	H	Br	Br	
H	H	H	Cℓ	NO_2	
H	H	H	Br	NH_2	
H	H	Me	Br	O^iPr	

Table II (continued)

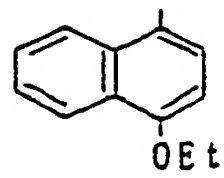
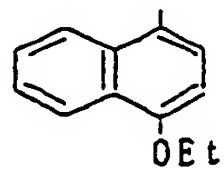
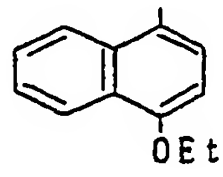
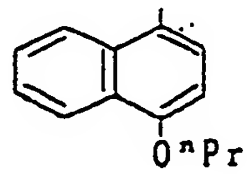
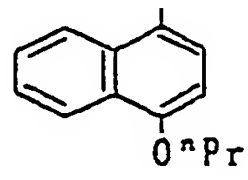
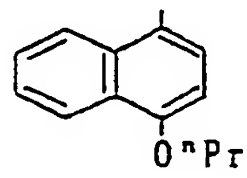
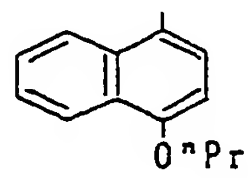
R_1	R_2	R_3	X	Y	Ar
Et	H	H	Cℓ	H	
^{i}Pr	H	H	Br	H	
	H	H	Br	H	
H	H	H	Cℓ	OMe	
H	H	H	Br	OEt	
H	H	H	Cℓ	O^{i}Pr	
H	H	H	Br	O^{sec}Bu	

Table II (continued)

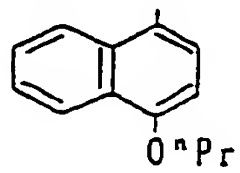
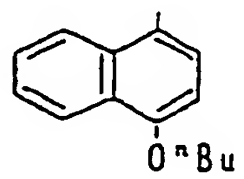
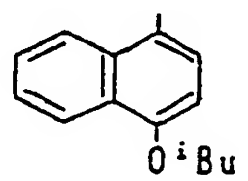
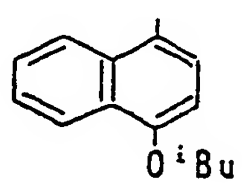
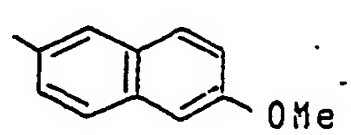
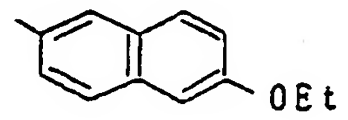
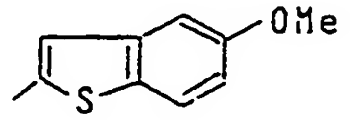
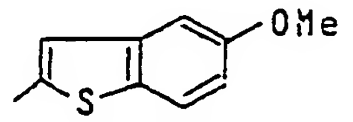
R_1	R_2	R_3	X	Y	Ar
H	H	H	Cℓ	O^nPr	
H	H	H	Cℓ	OEt	
H	H	H	Br	OEt	
H	H	H	Br	O^iBu	
H	H	H	Cℓ	OEt	
H	H	H	Br	O^iPr	
H	H	H	Cℓ	OEt	
H	H	Me	Br	O^iPr	

Table II (continued)

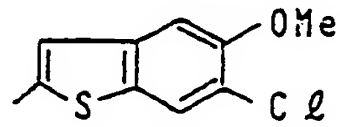
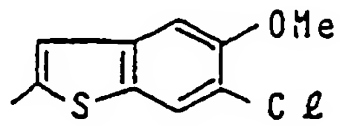
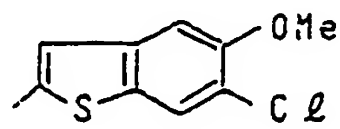
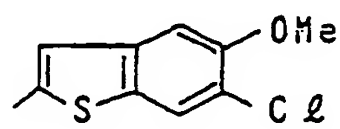
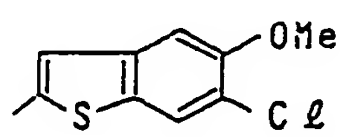
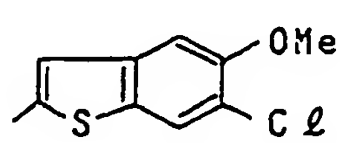
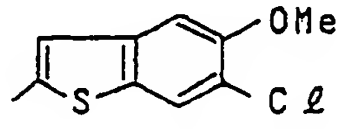
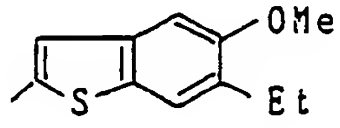
R_1	R_2	R_3	X	Y	Ar
H	H	H	Cℓ	H	
H	H	H	Cℓ	OMe	
H	H	H	Cℓ	OEt	
H	H	H	Cℓ	O^nPr	
H	H	H	Cℓ	O^nBu	
H	H	H	Cℓ	O^nHex	
H	H	H	Cℓ	O^nOct	
H	H	H	Cℓ	OEt	

Table II (continued)

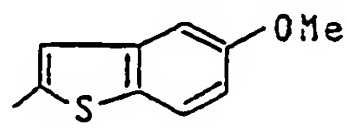
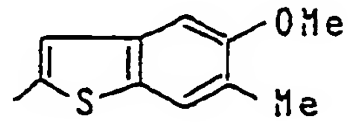
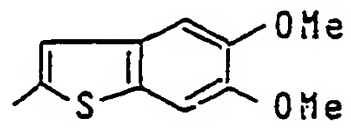
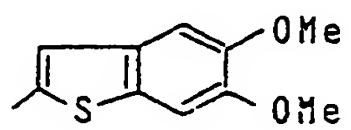
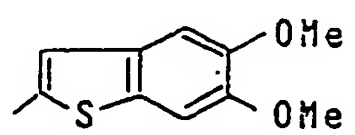
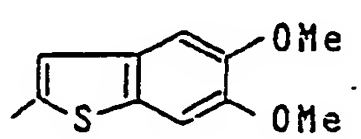
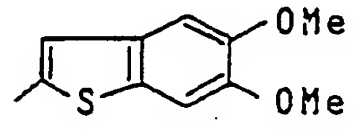
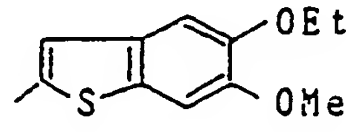
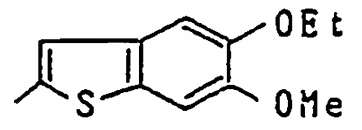
R_1	R_2	R_3	X	Y	Ar
H	H	H	Br	OEt	
H	H	H	Cℓ	H	
H	H	H	Br	OEt	
H	H	H	Br	H	
Et	H	H	Br	H	
^{i}Pr	H	H	Br	H	
	H	H	Br	H	
H	H	H	Cℓ	H	
H	H	H	Br	OEt	

Table II (continued)

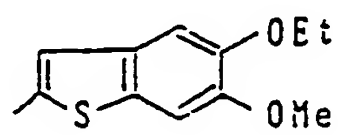
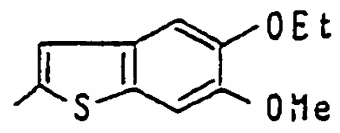
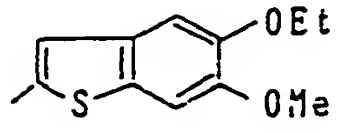
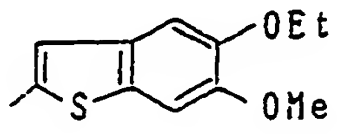
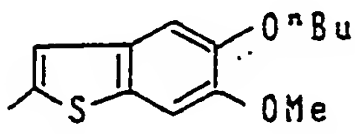
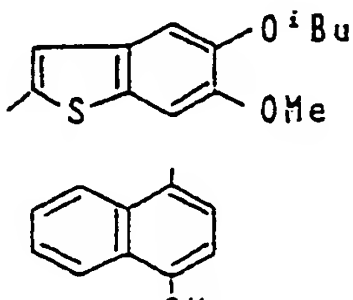
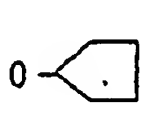
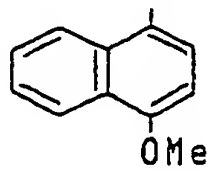
R_1	R_2	R_3	X	Y	Ar
H	H	H	Cℓ	O^iPr	
H	H	H	Br	Cℓ	
H	H	H	Cℓ	NO_2	
H	H	H	Br	SMe	
H	H	H	Br	OEt	
H	H	H	Br	O^iPr	
H	H	H	Br		
H	H	H	Br		

Table II (continued)

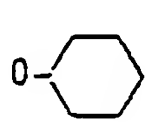
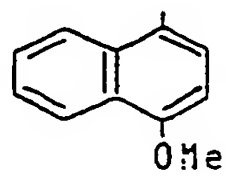
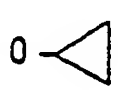
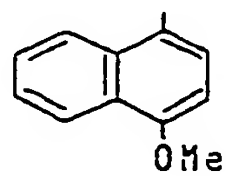
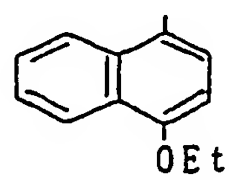
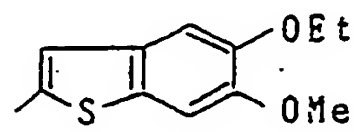
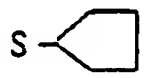
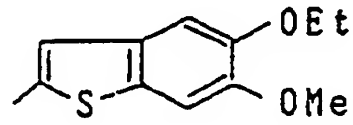
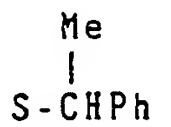
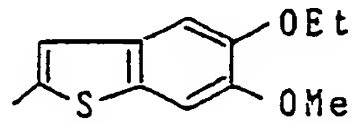
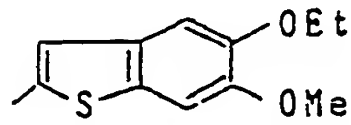
R_1	R_2	R_3	X	Y	Ar
H	H	H	Br		
H	H	H	Br		
H	H	H	Br	OCH_2Ph	
H	H	H	Br		
H	H	H	Br		
H	H	H	Br		
H	H	H	Br		

Table II (continued)

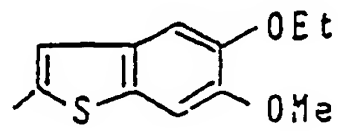
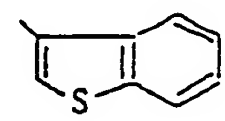
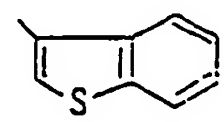
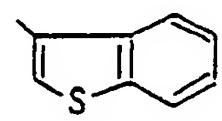
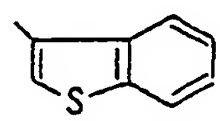
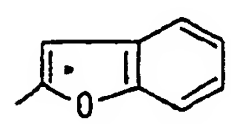
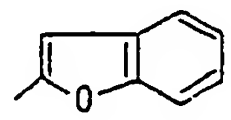
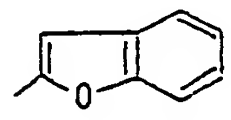
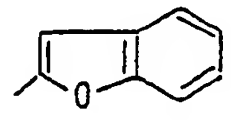
R_1	R_2	R_3	X	Y	Ar
H	H	H	Br	S^{sec}Bu	
H	H	H	Br	H	
H	H	H	Br	OMe	
H	H	H	Br	OEt	
H	H	H	Br	O^{i}Pr	
H	H	H	Br	H	
H	H	H	Br	NH_2	
H	H	H	Br	NO_2	
H	H	H	Br	OMe	

Table II (continued)

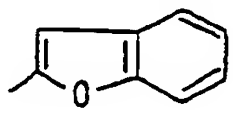
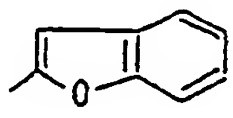
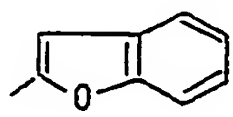
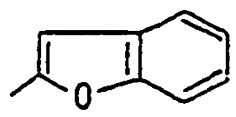
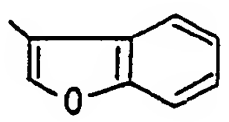
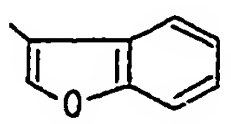
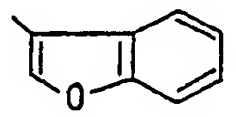
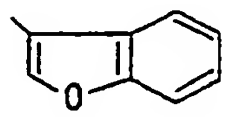
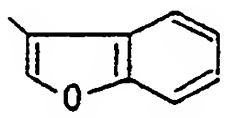
R_1	R_2	R_3	X	Y	Ar
H	H	H	Br	OEt	
H	H	H	Br	O^{i}Pr	
H	H	H	Br		
H	H	H	Br	Cℓ	
H	H	H	Br	H	
H	H	H	Br	OEt	
H	H	H	Br	O^{i}Pr	
H	H	H	Br	O^{sec}Bu	
H	H	H	Br	O- 	

Table II (continued)

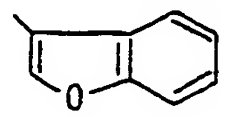
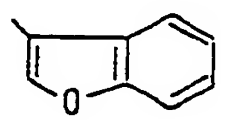
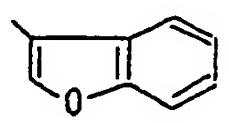
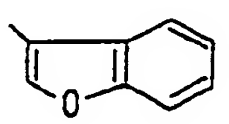
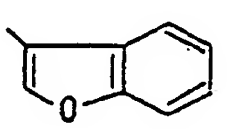
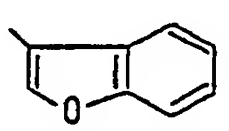
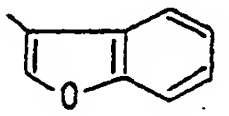
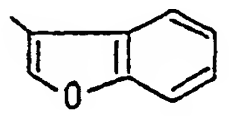
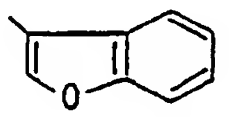
R_1	R_2	R_3	X	Y	Ar
H	H	H	Br	O-	
H	H	H	Br	NO_2	
H	H	H	Br	Cℓ	
H	H	H	Br	Br	
H	H	H	Br	Me | OCHPh	
H	H	H	Br	Et | OCHPh	
H	H	H	Br	SMe	
H	H	H	Br	SEt	
H	H	H	Br	Me | SCHPh	

Table II (continued)

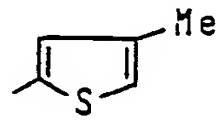
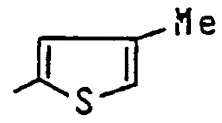
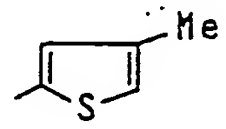
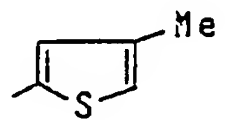
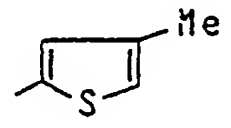
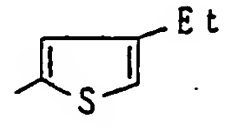
R_1	R_2	R_3	X	Y	Ar
H	H	H	Br	OEt	
H	H	H	Cℓ	O^{i}Pr	
H	H	H	Br	O^{sec}Bu	
H	H	H	Br		
H	H	H	Cℓ		
H	H	H	Br		
H	H	H	Br	Cℓ	
H	H	H	Br	NO_2	
H	H	H	Br	OEt	

Table II (continued)

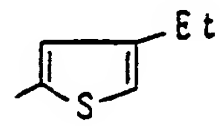
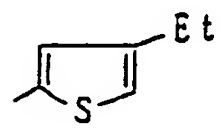
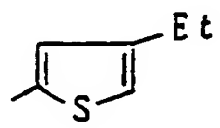
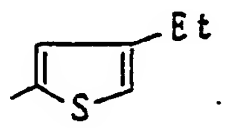
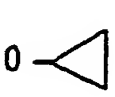
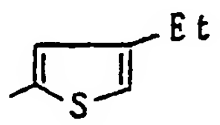
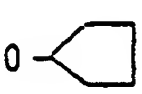
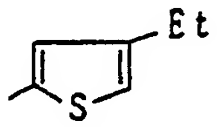
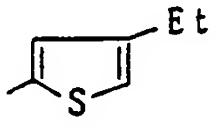
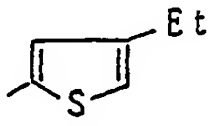
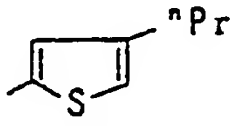
R_1	R_2	R_3	X	Y	Ar
H	H	H	Br	O^iPr	
H	H	H	Br	$O^{sec}Bu$	
H	H	H	Br	O^iHex	
H	H	H	Cℓ		
H	H	H	Br		
H	H	H	Cℓ		
H	H	H	Br	Cℓ	
H	H	H	Cℓ	NO_2	
H	H	H	Cℓ	OEt	

Table II (continued)

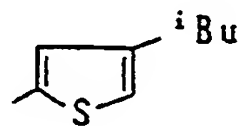
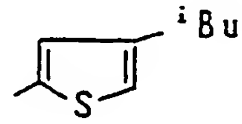
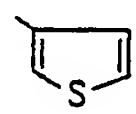
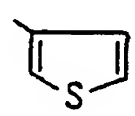
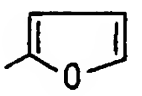
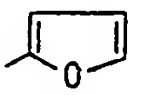
R_1	R_2	R_3	X	Y	Ar
H	H	H	Br	OEt	
H	H	H	Cℓ	O^{i}Pr	
H	H	H	Br	OEt	
H	H	H	Cℓ	O^{i}Pr	
H	H	H	Br	O^{sec}Bu	
H	H	H	Cℓ	O^{n}Pr	
H	H	H	Cℓ	NO_2	
H	H	H	Br	OEt	
H	H	H	Cℓ	O^{i}Pr	

Table II (continued)

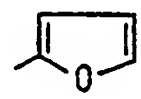
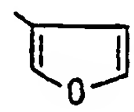
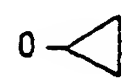
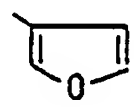
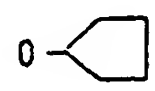
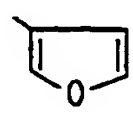
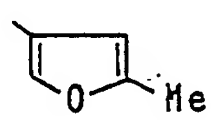
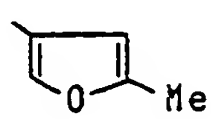
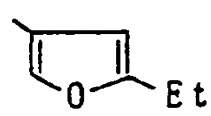
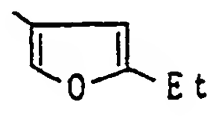
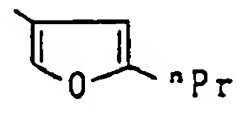
R_1	R_2	R_3	X	Y	Ar
H	H	H	Br	$O^{sec}Bu$	
H	H	H	Cℓ		
H	H	H	Br		
H	H	H	Cℓ		
H	H	H	Br	OEt	
H	H	H	Cℓ	$O^{i}Pr$	
H	H	H	Br	$O^{i}Pr$	
H	H	H	Cℓ	$O^{sec}Bu$	
H	H	H	Br	$O^{i}Bu$	

Table II (continued)

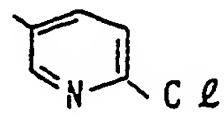
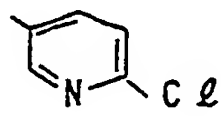
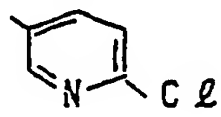
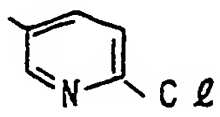
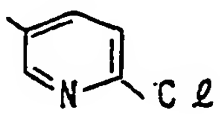
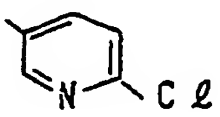
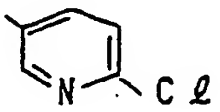
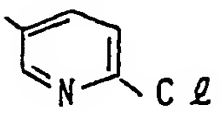
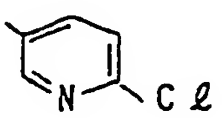
R_1	R_2	R_3	X	Y	Ar
H	H	H	Cℓ	Cℓ	
H	H	H	Cℓ	OEt	
H	H	H	Cℓ	O^{n}Pr	
H	H	H	Cℓ	O^{n}Pen	
H	H	H	Cℓ	O^{n}Hex	
H	H	H	Cℓ	O^{n}Oct	
H	H	H	Cℓ		
H	H	H	Cℓ	SEt	
H	H	H	Cℓ	OCHPh | Me	

Table II (continued)

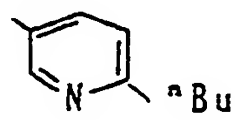
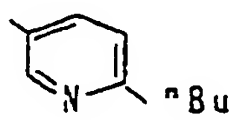
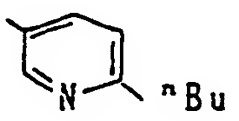
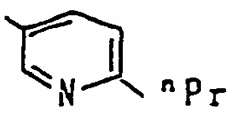
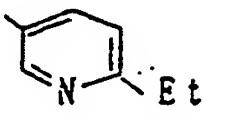
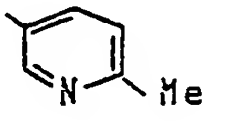
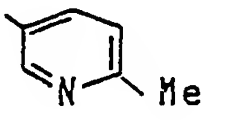
R_1	R_2	R_3	X	Y	Ar
H	H	H	Br	OMe	
H	H	H	Br	OEt	
H	H	H	Br	O^{n}Pr	
H	H	H	Br	O^{i}Pr	
H	H	H	Br	O^{n}Bu	
H	H	H	Br	O^{n}Bu	
H	H	H	Br	OCHPh | Me	

Table II (continued)

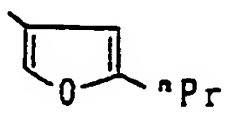
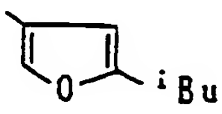
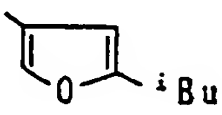
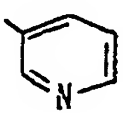
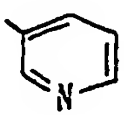
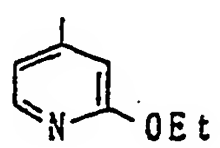
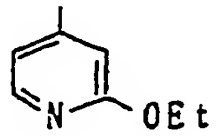
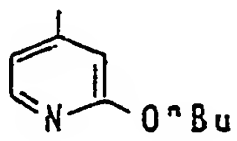
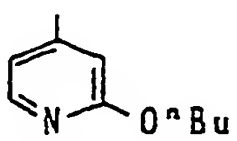
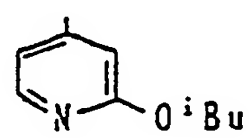
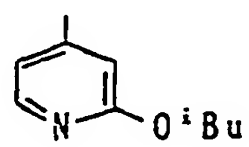
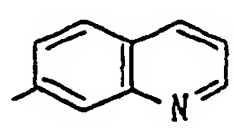
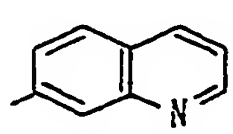
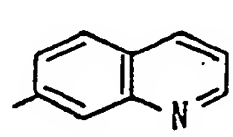
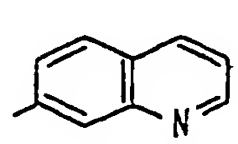
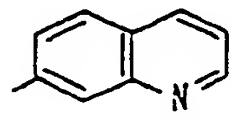
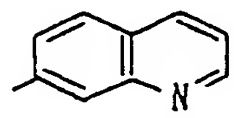
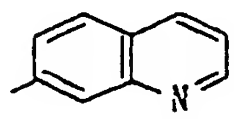
R_1	R_2	R_3	X	Y	Ar
H	H	H	Cℓ	O^iPen	
H	H	H	Br	OEt	
H	H	H	Cℓ	O^iPr	
H	H	H	Br	OEt	
H	H	H	Cℓ	O^iPr	
H	H	H	Br	OEt	
H	H	H	Cℓ	O^iPr	
H	H	H	Br	OEt	
H	H	H	Cℓ	O^iPr	

Table II (continued)

R_1	R_2	R_3	X	Y	Ar
H	H	H	Br	OEt	
H	H	H	Cℓ	O^{i}Pr	
H	H	H	Cℓ	NO_2	
H	H	H	Cℓ	Cℓ	
H	H	H	Cℓ	NH_2	
H	H	H	Cℓ	OMe	
H	H	H	Cℓ	SMe	
H	H	H	Cℓ	OEt	
H	H	H	Cℓ	O^{i}Pr	

Now, Formulation Examples will be given.

FORMULATION EXAMPLE 1 (Tablets)	
Compound No. 31	10 g
Lactose	20 g
Starch	4 g
Starch for paste	1 g
Magnesium stearate	100 mg
Carboxymethyl cellulose calcium	7 g
Total	42.1 g

The above components were mixed in a usual manner, and formulated into sugar-coated tablets each containing 50 mg of an active ingredient.

FORMULATION EXAMPLE 2 (Capsules)	
Compound No. 5	10 g
Lactose	20 g
Crystal cellulose powder	10 g
Magnesium stearate	1 g
Total	41 g

The above components were mixed in a usual manner, and filled into gelatin capsules to obtain capsules each containing 50 mg of an active ingredient.

FORMULATION EXAMPLE 3 (Soft capsules)	
Compound No. 36	10 g
Corn Oil	35 g
Total	45 g

The above components were mixed and formulated in a usual manner to obtain soft capsules.

FORMULATION EXAMPLE 4 (Ointment)	
Compound No. 16	1.0 g
Oilve Oil	20 g
White vaseline	79 g
Total	100 g

The above components were mixed in a usual manner to obtain 1% ointment.

FORMULATION EXAMPLE 5 (Aerosol suspension)		
(A)	Compound No. 34	0.25 (%)
	Isopropyl myristate	0.10
	Ethanol	26.40
(B)	A 60-40% mixture of 1,2-dichlorotetrafluoroethane and 1-chloropentafluoroethane	73.25

The above composition (A) was mixed. The solution mixture thereby obtained was charged in a container equipped with a valve, and the propellant (B) was injected from the valve nozzle to a gauge pressure of from about 2.46 to 2.81 mg/cm^2 to obtain an aerosol suspension.

TEST EXAMPLES

A. Antagonistic activity test against SRS-A

SRS-A is a mixture of LTC_4, LTD_4, LTE_4 and the like. Accordingly, antagonistic activities against SRS-A can be evaluated by one of the following two test methods:

(1) A method of examining the antagonistic activities against SRS-A obtained from a sensitized guinea-pig,

(2) A method of examining the antagonistic activities against LTC_4, LTD_4 or LTE_4.

The present inventors examined the antagonistic activities of compounds of the formula I against SRS-A by using the following test methods.

1) Test methods

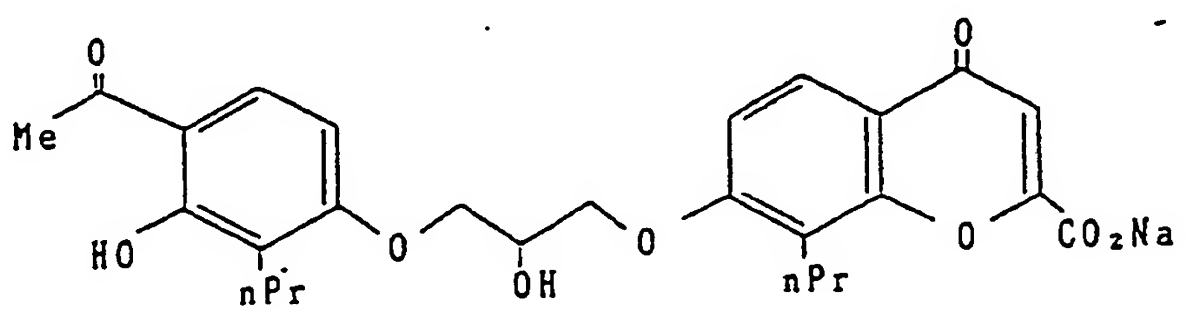
(1) in vitro test

LTD_4 antagonism in guinea-pig trachea

Antagonism for LTD_4 was determined in isolated male guinea-pig (300 - 400 g) trachea prepared as spiral strip. Tracheal preparations were suspended under 1 g tension in 10 ml organ baths containing 5 μM of indomethacin and they were incubated for 1 hour prior to used. Contractile responses to LTD_4 (2×10^{-8} g/ml) were obtained after the maximal response to histamine (10^{-4} M). Test compounds dissolved in 100% dimethyl sulfoxide were added to the organ baths (final concentration of 10^{-6} g/ml) 30 min prior to LTD_4 addition, and then contractile responses to LTD_4 were compared with those of control which was obtained from a paired trachea in the absence of test compounds. LTD-induced contractions were expressed as a percentage of the maximal response to histamine. The antagonism was determined as follows:

Antagonism (%) = (1.0 - contraction in test/% contraction in control) x 100

FPL-55712 (Fisons Limited) approved as a selective SRS-A antagonist, was used as the control.



FPL－55712

(2) in vivo test

Effect on anaphylactic bronchoconstriction mediated by endogeneously liberated SRS-A in passively sensitized guinea-pig

Male guinea-pigs (350 - 450 g) were passively sensitized with intravenous (iv.) injection of 0.125 ml rabbit anti-EA (egg albumin) serum (Capple Laboratories) 1 to 2 days preceding the experiment. Antigen-induced anaphylactic bronchoconstrictions mediated by endogeneously liberated SRS-A were measured by modified method of Konzett and Rossler (Arch. Exp. Path. Pharmak., 195, 71, 1940). Sensitized guinea-pigs were anaesthetized with intraperitoneal injection of urethane (1.5 g/kg). The right jugular vein was cannulated for the administration of the all agents and trachea was cannulated to record total pulmonary resistance. guinea-pigs were artificially ventilated by a small animal respirator (Shinano, Model SN-480-7) set at a stroke volume of 4.5 ml and a rate of 50 breaths per min. The change in pulmonary resistance was

measured with a pressure transducer (Nihon Kohden, Model TP-602T) connected to a T-tube on the tracheal cannula. The percentage of the maximum bronchoconstriction obtained by clamping off the trachea. Following surgical preparation, the animals were pretreated with indomethacin (2 mg/kg, 10 min), pyrilamine (2 mg/kg, 6 min) and propranolol (0.1 mg/kg, 5 min) prior to the EA challenge (0.2 mg/kg). All test compounds were administered orally 2 hours before the EA challenge. Inhibition (%) of bronchoconstriction was determined as follows: Inhibition (%) = (1.0 - % maximum bronchoconstriction in test/% maximum bronchoconstriction in control) x 100. The maximum bronchoconstriction was 62 ± 6% (Mean ± S.E.M; n = 6) and the number of test animals was 5 - 6.

2) Test results

(1) in vitro test

LTD_4 antagonisms by test compounds at a concentration of 10^{-6} g/ml are shown in Table III.

Table III

Test compound No.	Antagonism (%)	Test compound No.	Antagonism (%)
5	79	31	95
16	74	32	50
22	39	34	99
23	57	38	43
24	67	57	69
25	50	60	96
30	50	FPL-55712	94

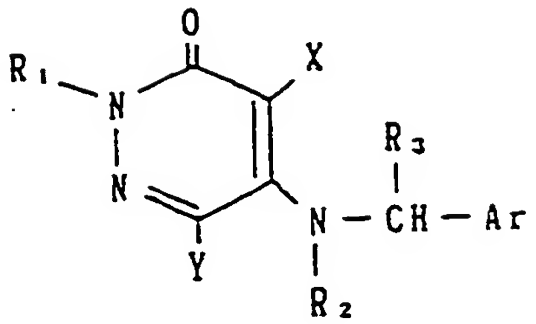
(2) in vivo test

Each of tested 3(2H)pyridazinones of the formula I and pharmaceutically acceptable salts as representative compounds of the present invention showed significant inhibitory effects over the control at a dose of 100 mg/kg by oral administration.

From these results, it is evident that the compounds of the present invention exhibit prominent antagonistic activities against SRS-A and its major constituents LTC_4 and LTD_4 in vitro and in vivo. Therefore, the compounds of the present invention are expected to be useful, as prophylactic and therapeutic drugs against various immediate type allergic diseases such as bronchial asthma, allergic rhinitis, urticaria and hay fever, various inflamatory diseases such as rheumatoid arthritis and spondyloarthritis, or ischemic heart diseases such as angina pectoris and myocardial infarction, induced by SRS-A or by one of LTC_4, LTD_4 and LTE_4 as its constituents or a mixture thereof.

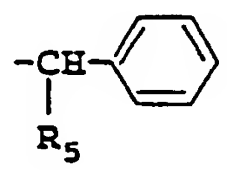
Claims

1. A 3(2H)pyridazinone of the formula:

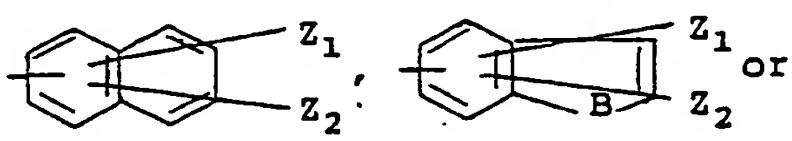


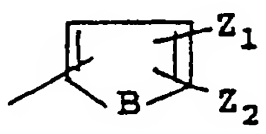
(I)

wherein R_1 is hydrogen, 2-propenyl, or straight chained or branched C_1-C_4 alkyl; each of R_2 and R_3 which may be the same or different, is hydrogen, or straight chained or branched C_1-C_3 alkyl; X is chlorine, or bromine; Y is hydrogen, halogen, nitro, amino, or $-AR_4$ wherein A is oxygen, or sulfur, and R_4 is hydrogen, straight chained, branched or cyclic C_1-C_8 alkyl, or



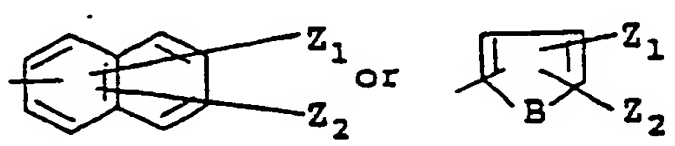
wherein R_5 is hydrogen, or straight chained or branched C_1-C_4 alkyl; and Ar is





wherein each of Z_1 and Z_2 which may be the same or different, is hydrogen, halogen, straight or branched C_1-C_4 alkyl, or $-OR_6$ wherein R_6 is straight or branched C_1-C_4 alkyl, and B is oxygen, sulfur, or -N=C- (to form a quinoline or pyridine ring); or a pharmaceutically acceptable salt thereof.

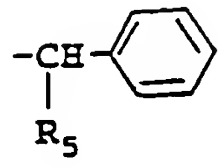
2. The 3(2H)pyridazinone according to Claim 1, wherein Ar is



wherein each of Z_1 and Z_2 which may be the same or different, is hydrogen, halogen, straight chained or branched C_1-C_4 alkyl, or $-OR_6$ (wherein R_6 is straight chained or branched C_1-C_4 alkyl, and B is oxygen, sulfur, and -N=C- (to form a pyridine ring), or a pharmaceutically acceptable salt thereof.

3. The 3(2H)pyridazinone according to Claim 1, wherein R_3 is hydrogen, or a pharmaceutically acceptable salt thereof.

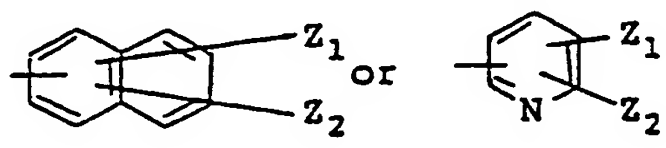
4. The 3(2H)pyridazinone according to Claim 3, wherein Y is hydrogen, halogen, nitro, amino, or $-OR_4$ wherein R_4 is hydrogen, straight chained, branched or cyclic C_1-C_8 alkyl, or



wherein R_5 is hydrogen, or straight chained or branched C_1-C_4 alkyl, or a pharmaceutically acceptable salt thereof.

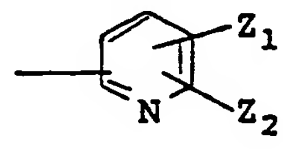
5. The 3(2H)pyridazinone according to Claim 4, wherein R_2 is hydrogen, and y is hydrogen, chlorine, nitro, amino, or -OR_4 wherein R_4 is straight chained or branched C_1-C_8 alkyl, C_3-C_6 cycloalkyl, or benzyl, or a pharmaceutically acceptable salt thereof.

6. The 3(2H)pyridazinone according to Claim 5, wherein Ar is



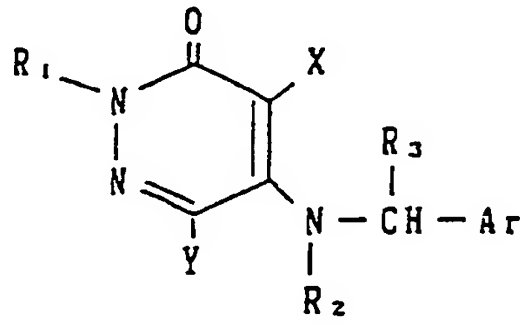
wherein each of Z_1 and Z_2 which may be the same or different, is hydrogen, chlorine, straight chained C_1-C_4 alkyl, or -OR_6 wherein R_6 is straight chained C_1-C_4 alkyl, or a pharmaceutically acceptable salt thereof.

7. The 3(2H)pyridazinone according to Claim 6, wherein Ar is



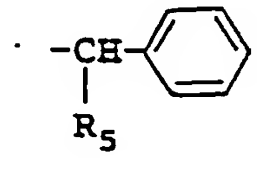
wherein each of Z_1 and Z_2 which may be the same or different, is hydrogen, chlorine, or -OR_6 wherein R_6 is straight chained or branched C_1-C_4 alkyl, or a pharmaceutically acceptable salt thereof.

8. A process for producing a 3(2H)pyridazinone of the formula:

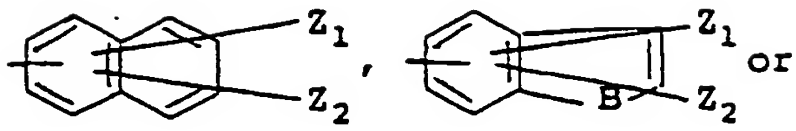


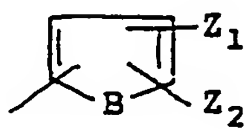
(I)

wherein R_1 is hydrogen, 2-propenyl, or straight chained or branched C_1-C_4 alkyl; each of R_2 and R_3 which may be the same or different, is hydrogen, or straight chained or branched C_1-C_3 alkyl; X is chlorine, or bromine; Y is hydrogen, halogen, nitro, amino, or -AR_4 wherein A is oxygen, or sulfur, and R_4 is hydrogen, straight chained, branched or cyclic C_1-C_8 alkyl, or

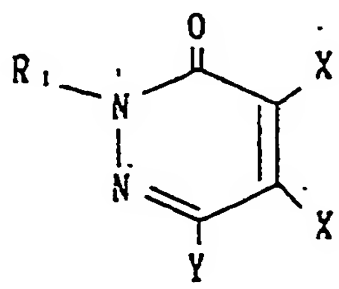


wherein R_5 is hydrogen, or straight chained or branched C_1-C_4 alkyl; and Ar is



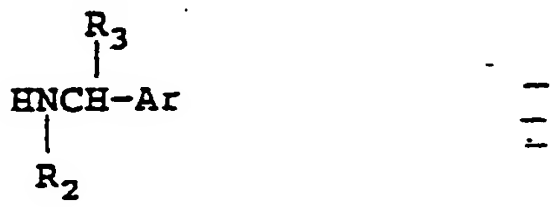


wherein each of Z_1 and Z_2 which may be the same or different, is hydrogen, halogen, straight or branched C_1-C_4 alkyl, or -OR_5 wherein R_5 is straight or branched C_1-C_4 alkyl, and B is oxygen, sulfur, or -N=C- (to form a quinoline or pyridine ring); or a pharmaceutically acceptable salt thereof, which comprises reacting a 4,5-dihalo-3(2H)pyridazinone compound of the formula:



(IIA)

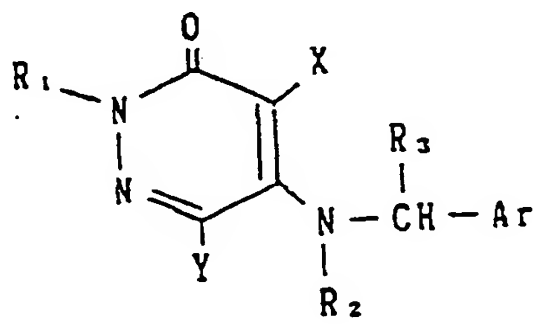
wherein R_1, X and Y are as defined above, with an arylmethylamino compound of the formula:



(III)

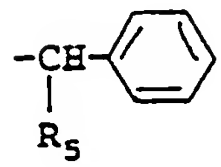
wherein R_2, R_3 and Ar are as defined above, or its salt, if necessary in the presence of an acid binding agent.

9. A process for producing a 3(2H)pyridazinone of the formula:

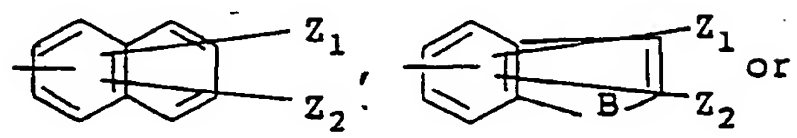


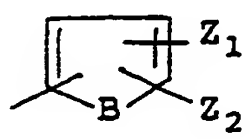
(I)

wherein R_1 is hydrogen, 2-propenyl, or straight chained or branched C_1-C_4 alkyl; each of R_2 and R_3 which may be the same or different, is hydrogen, or straight chained or branched C_1-C_3 alkyl; X is chlorine, or bromine; Y is hydrogen, halogen, nitro, amino, or -AR_4 wherein A is oxygen, or sulfur, and R_4 is hydrogen, straight chained, branched or cyclic C_1-C_8 alkyl, or

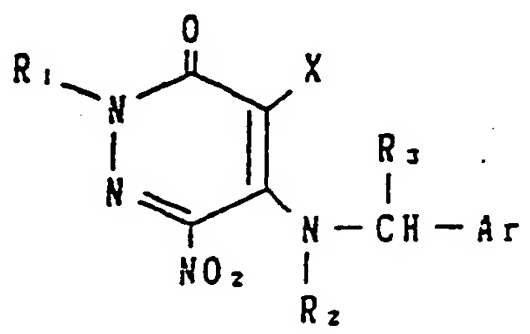


wherein R_5 is hydrogen, or straight chained or branched C_1-C_4 alkyl; and Ar is





wherein each of Z_1 and Z_2 which may be the same or different, is hydrogen, halogen, straight or branched C_1-C_4 alkyl, or -OR_6 wherein R_6 is straight or branched C_1-C_4 alkyl, and B is oxygen, sulfur, or -N=C- (to form a quinoline or pyridine ring); or a pharmaceutically acceptable salt thereof, which comprises reacting a 6-nitro-5-arylmethylamino compound of the formula:



(IB-a)

wherein R_1, R_2, R_3, X and Ar are as defined above, with an alkali metal salt of the formula:
$M^{\oplus}AR_4^{-}$ (IV)
wherein M is alkali metal, and A and R_4 are as defined above.

10. An antagonistic agent against SRS-A comprising an effective amount of a 3(2H)pyridazinone of the formula I as defined in Claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 12 3159

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A,D	EP-A-0 186 817 (NISSAN CHEMICAL INDUSTRIES LTD) * Claims * ---	1,8,10	C 07 D 237/22 A 61 K 31/50 C 07 D 405/12 C 07 D 409/12 C 07 D 401/12
A,D	EP-A-0 275 997 (NISSAN CHEMICAL INDUSTRIES LTD) * Claims * ---	1,8-10	
A	EP-A-0 199 281 (NISSAN CHEMICAL INDUSTRIES LTD) * Claims * -----	1	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C 07 D 237/00
A 61 K 31/00
C 07 D 405/00
C 07 D 401/00
C 07 D 409/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	19-03-1990	DE JONG B.S.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)